A USEFUL SYNTHON FOR ELABORATION INTO IRIDOIDS AND ALKALOIDS

BY

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ABSTRACT

The iridoid compound, secologanin, is known to be a precursor of the antitumor drug camptothecin, which is obtained from the tree, Camptotheca acuminata.

Starting from furfuryl alcohol, an efficient preparation of the 3,4-dihydro synthon (7A) of secologanin aglucone was accomplished. Our synthesis utilizes a Diels-Alder reaction of butadiene with 4,5-dehydro-pyran-6-methoxy-3-one (94) to yield cis-7,8-dehydro-1-methoxy-2-oxa-4-decalone, 41A. This was converted to the C-4 nitrile, 98, by a one carbon homologation using the tosylmethyl isocyanide reagent. The nitrile 98 was converted to methyl ester 7A by an extremely mild, three step procedure.

Investigations into the bridgehead stereochemistry of the key intermediate, 41A, and the literature intermediate, 88 (reportedly also a cis fused, bicyclic ketone), revealed that the earlier work was incorrect regarding the bridgehead stereochemistry of 88. In addition to giving the correct stereoisomer, this work details a much more efficient synthesis of the 3,4-dihydro secologanin aglucone synthon than the method which we had originally published.

Approved_____

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Date _____

To Leslie

ACKNOWLEDGEMENTS

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Finally, I would like to express my gratitude to my parents, Mr. and Mrs. A.B. Sisk and grandparents, Mr. and Mrs. D. Sisk, for their support.

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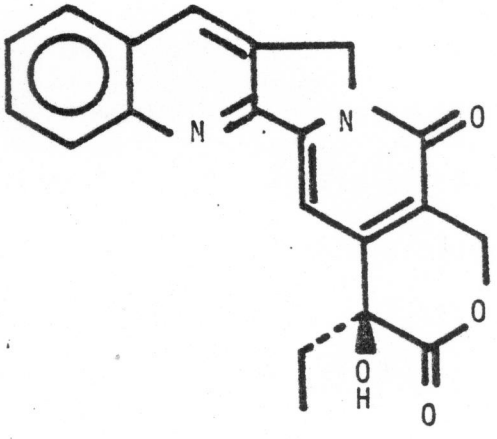
I. Introduction

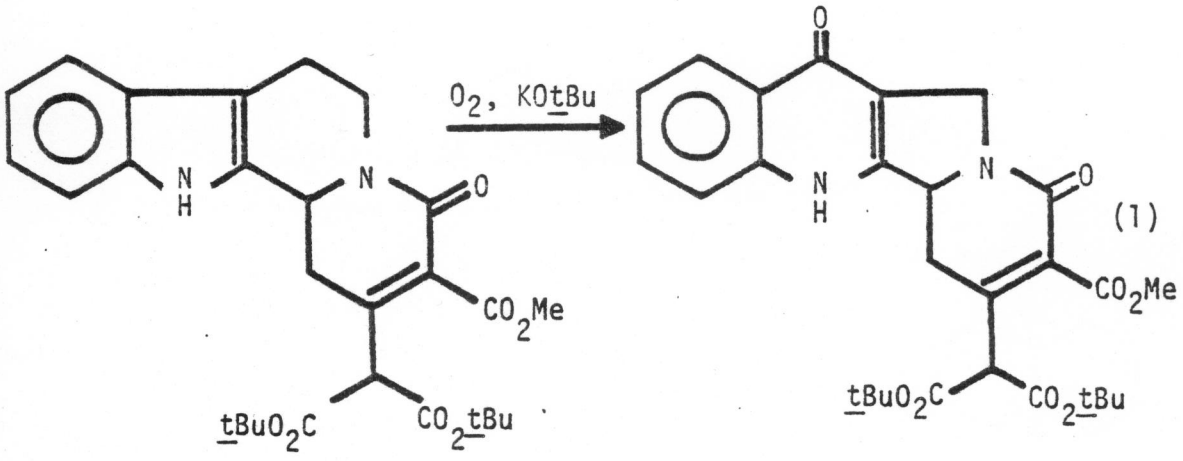
The antitumor alkaloid, camptothecin (1), was isolated from the Chinese tree, Camptotheca acuminata (NYSSACEAE), and characterized by Wall and co-workers in 1966.[3,4] It has been the goal of many chemical syntheses because it is difficult to extract the material from the natural source in adequate yield for evaluation of its antitumor properties. Also, it is a problem to maintain a good supply of the plant material, since it mainly grows in China.[1,2]



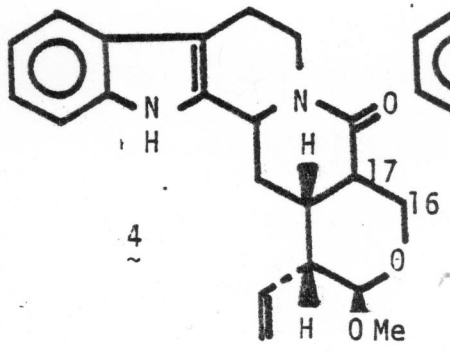
Camptothecin 1

(1)

This alkaloid, unusual because of its pyrrolo [3,4-b] quinoline ring system, was first synthesized by Schultz and Stork in 1971.[5] Winterfeldt later developed a biogenetically oriented synthesis based upon an indole to quinoline conversion (2 to 3), eq. 1, which he believed also occurred naturally.



In our laboratories, we are also developing a biomimetic approach towards the synthesis of camptothecin and its analogs. Our research is medicinally and biosynthetically oriented. We hope to develop a 16, 17-dihydro analog, 4, of strictosamide (5) for biosynthetic experiments. Additionally, we feel our approach will lead to a facile preparation of campothecin analogs that will enable us to help define the drug's mechanism of action.



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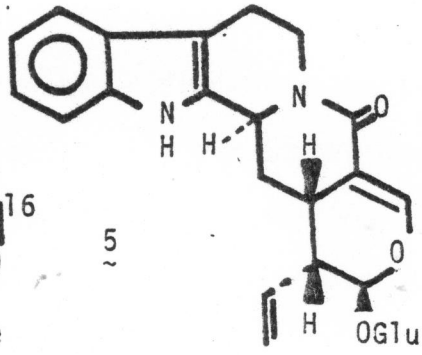
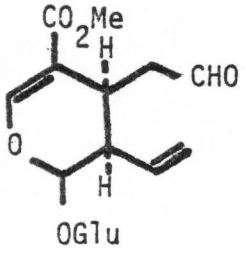


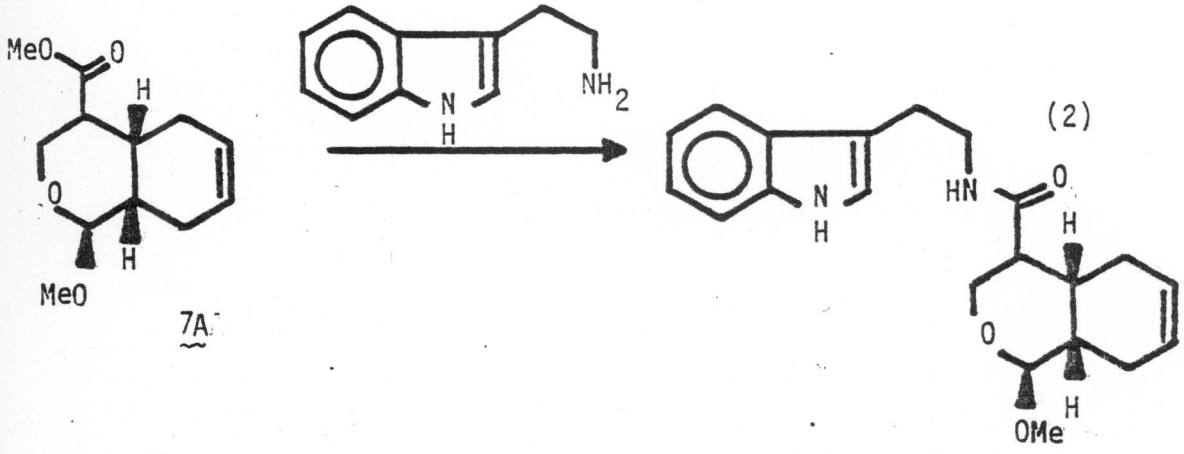
5

Strictosamide



6

Secologanin



Our general approach will utilize the condensation of a secologanin analog, 7, with tryptamine (eq. 2).[12] This secologanin analog should be more advantageous to our plan then secologanin (6) itself because secologanin is very hard to remove from its glucose without extensive rearrangement, although it is easily obtainable from natural sources.[8,9] The 2-oxa-decalin synthon, 7A provides a method for preparation of the 16, 17-dihydro-strictosamide analogs (4) which we desire for biosynthetic studies, as well as giving us a useful synthon for other alkaloids and cyclopentanomonoterpenoids.[10,11]

This synthon, 7A is especially attractive because the research described in this thesis proved that 7A could be efficiently obtained from an inexpensive starting material, furfuryl alcohol

II. Background

A. Camptothecin's Antitumor Properties

Camptothecin has never enjoyed much success in the United States as a clinical chemotherapeutic agent. Despite findings showing that the drug has antitumor properties in laboratory animals and one report of its effectiveness in the treatment of advanced gastrointestinal carcinoma, there is some evidence citing the overall inefficacy and toxic side effects associated with its clinical usage.[44-46, 13, 14]

The Chinese have used this drug in conjunction with ammonium glycyrhetinate and are reported to have had good results in the treatment of gastrointestinal carcinoma.[15] Although clinically inappropriate, camptothecin has been found to have some interesting biochemical interactions, the study of which may eventually lead to clinically acceptable analogs.[47]

The chemotherapeutic mode of action of camptothecin seems to be to reduce biosynthesis and hasten degradation of higher molecular weight DNA polymers. However, no study has clearly shown that camptothecin is effective as an antitumor drug because of this property. Researchers have found that the drug inhibited the biosynthesis of polynucleotides in HeLa and L-1210 leukemia cells.[16,17] For example, HeLa cells exhibited a 50% inhibition of DNA and RNA synthesis when treated with five micromolar comptothecin.[18] Horwitz demonstrated that the compound has a differential effect upon the

type of RNA synthesized: higher molecular weight RNA and ribosomal RNA were affected the most.[18] Other investigators have shown that a mononucleic acid synthesis, the activity of DNA and RNA polymerases, and certain DNA repair enzymes were not altered by camptothecin.[16,19] Moreover, in the case of RNA, and to a lesser extent, DNA biosynthesis, removal of camptothecin from the media led to a rapid resumption of normal RNA synthesis.[18] This seems to indicate that there was a freely reversible association of camptothecin and the polynucleotide. During this association some type of inhibition of replication occurs.

It seems that the most probable cause of the inhibition of polynucleotide biosynthesis is due to production of single strand nicks in the DNA, as was observed in the DNA isolated from intact, treated HeLa and L-1210 leukemia cells.[48] DNA nicking, by camptothecin alone, has been observed in intact cells, but doesn't appear to occur in the isolated nuclei or mitochondria of cells.[19,49] Horwitz et al. have shown that the inhibition of polymerization is reversible.[18,48] This may be due to repair of the nicked DNA template but no clear evidence has been presented.[18] The resumption of synthesis was taken as an indication that no permanent binding of the drug to DNA occurs.

Using a very sensitive electrophoretic assay for DNA nicking, Dr. Howard Gamper of the University of California, Berkeley, tested the ability of camptothecin to nick highly purified superhelical Col E-I DNA. His results showed that no nicking occurred under his

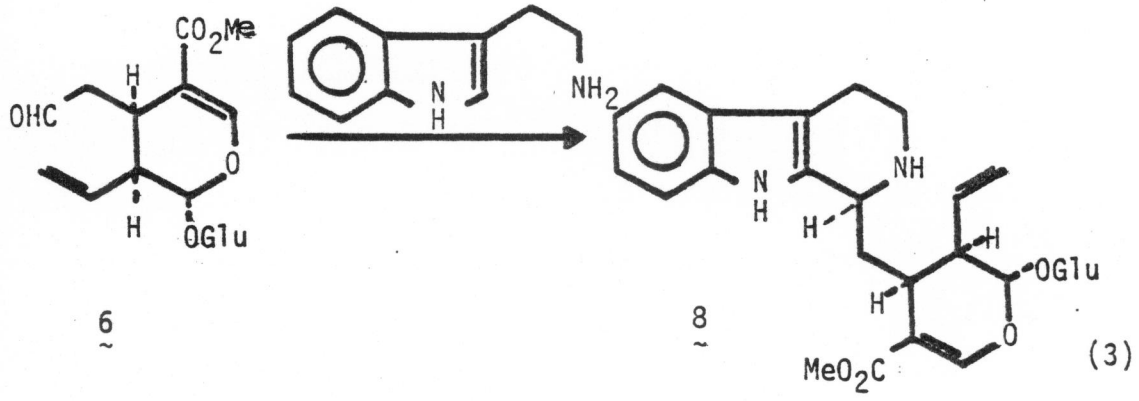
experimental conditions. Professor J.W. Lown, of the University of Alberta, has had similar results using a different system to assay the effect of camptothecin upon isolated PM-2 covalently closed circular DNA.[21]

It may be that nicking occurs only in vivo. For example, it may depend on some form of cellular activation of camptothecin to produce $O_2^{\cdot-}$, which could be the nicking species, as it is in the case of bleomycin, adriamycin and streptonigrin.[15] Another explanation of why polynucleotides are only nicked by camptothecin in intact cellular systems could be the possibility of a second component present in the cytoplasm (or nucleus) which influences polynucleotide binding or drug activation in some other way than superoxide formation. When the polynucleotide is purified this factor is lost and camptothecin is rendered, essentially, inactive.

B. Properties of Some Cyclopentanomonoterpenoids Related to Secologanin.

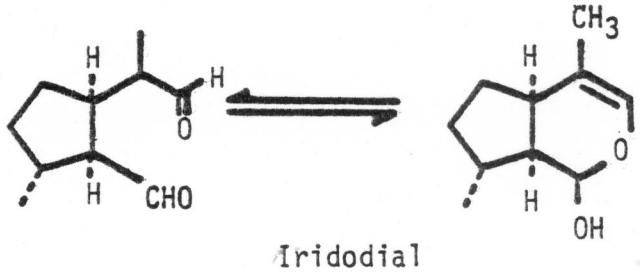
Camptothecin and many other indole alkaloids from higher plants, are considered to form by way of a Mannich condensation between tryptamine and secologanin (eq. 3).[23,24] One of the key biosynthetic precursors has been shown to be strictosidine (8).

After illustrating the biosynthesis of secologanin (6), I will consider its incorporation into camptothecin in greater depth.



6 8 (3)

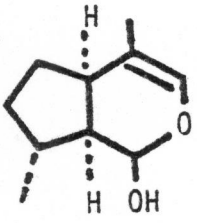
Iridoids, also known as cyclopentanomonoterpenoids, are a large class of naturally occurring compounds. Secologanin is a member of this chemical classification because of its derivation from loganin (possibly by way of eq. 6).[36] These substances are oxygenated, cyclic monoterpenes with a close structural similarity to iridodial, 9 (shown in eq. 4 as hemiacetal and open forms).



(4)

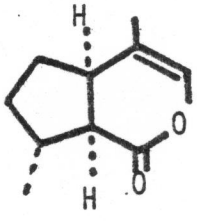
Iridodial

Iridoids were so named from the early discovery of iridomyrmecin, iridolactone and iridodial in the defensive secretions of the stinging ant, Iridomyrmex sp.[35] Subsequently, these and many close analogs were found to be widely distributed throughout the plant kingdom. When iridoids are found in plants, it is usually as the β-glucoside, not the free hemiacetal, as in iridodial (9).[36]

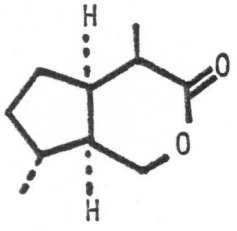


Iridodial

(9)



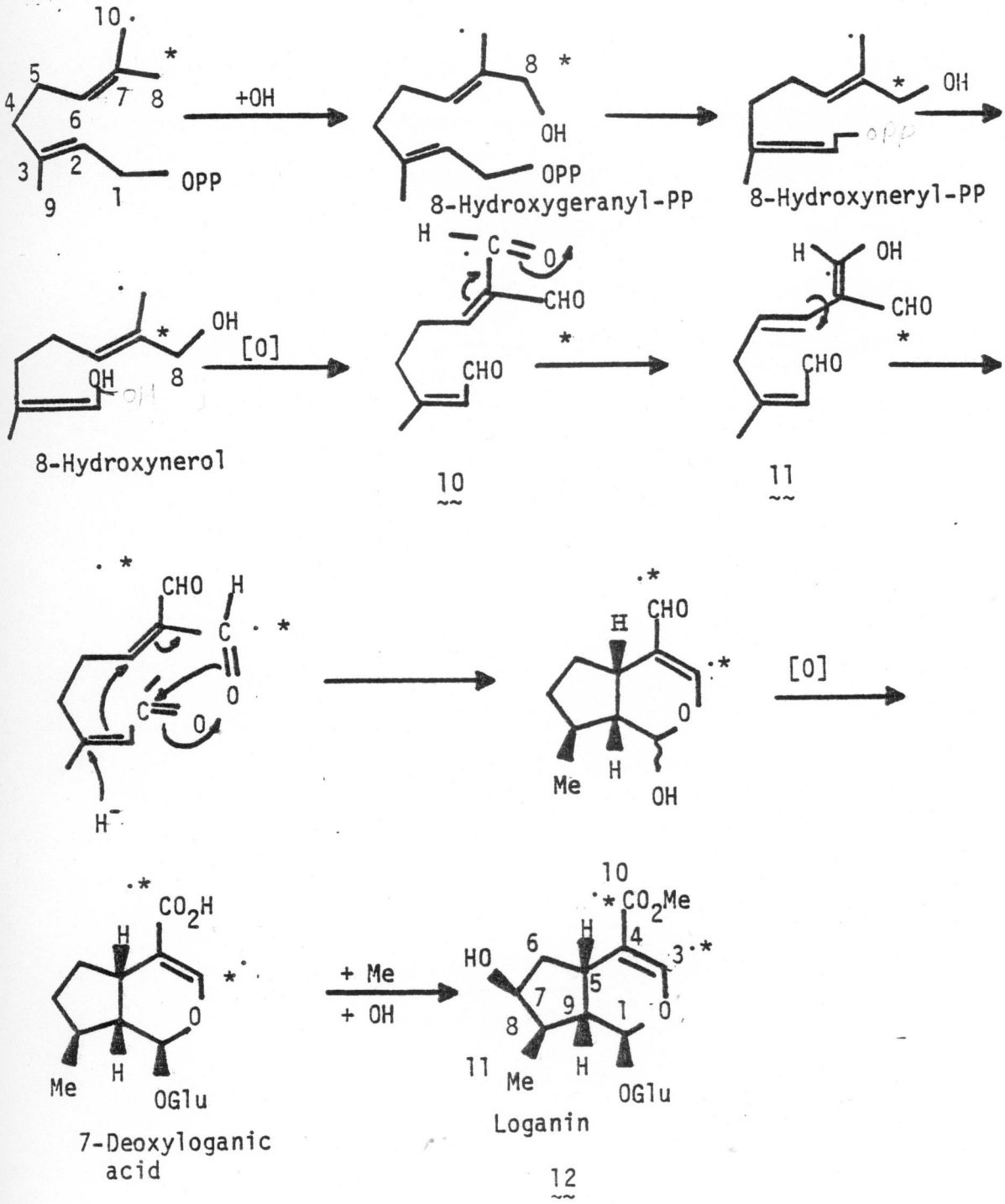
Iridolactone



Iridomyrmecin

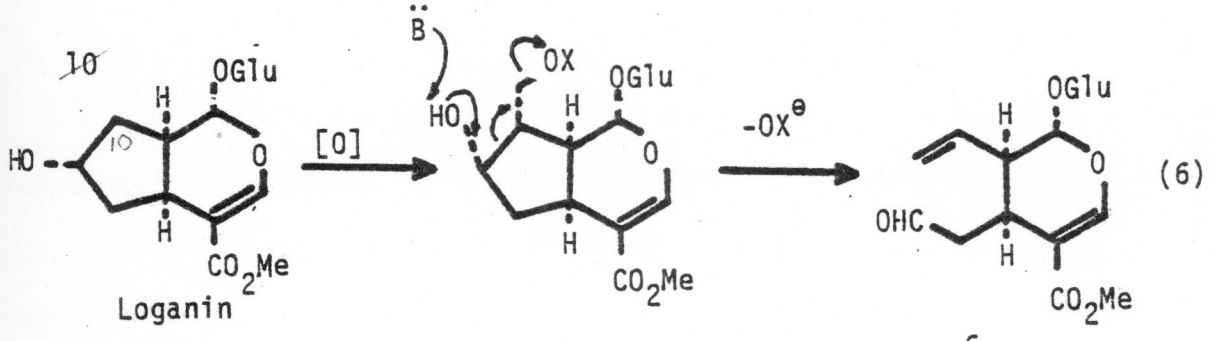
Numerous experiments involving feeding radioactively labelled precursors to plants have demonstrated that iridoids are derived directly from mevalonic acid via geranyl/nerol pyrophosphate (eq. 5).[50] It was found that geranyl pyrophosphate was hydroxylated at the C-10 position and the E-olefin isomerized to give, after pyrophosphate cleavage, 10-hydroxynerol. Although not proven, it is felt that a second hydroxylation at C-8, followed by oxidation, leads to a trialdehyde (10, eq. 5).[37] When geranyl pyrophosphate was labelled at either the C-8 or C-10 position, the iridoid formed as a result of

Eq. 5


10
5
4
6
7
8
3
2
9
1
OPP
+OH
8
OH
OPP
8-Hydroxygeranyl-PP
OH
OPP
8-Hydroxyneryl-PP
OH
[O]
OH
8
8-Hydroxynerol
H
C
O
CHO
CHO
10
H
OH
CHO
CHO
11
CHO
H
C
O
C
O
H
O
Me
H
OH
[O]
CO2H
H
O
Me
H
OGlu
7-Deoxyloganic acid
+ Me
+ OH
10
CO2Me
H
HO
6
4
3
5
7
9
1
8
O
11
Me
H
OGlu
Loganin
12

its incorporation may be equally labelled at positions three and ten. This has been explained on the basis that isomerization takes place by way of an intermediate enol compound (11, eq. 5). Reductive cyclization of the trialdehyde, followed by C-1 glucosylation and C-10 oxidation leads to 7-deoxyloganic acid. Methyl esterification of the acid, and C-7 hydroxylation gives loganin (12).

It is thought that most of the iridoids are derived from 7-deoxyloganic acid or loganin by appropriate biosynthetic modifications.[38] A pertinent example is secologanin, eq. 6. Loganin is possibly converted to secologanin by hydroxylation of the C-10 position, perhaps by the addition of a suitable leaving group (phosphate has been suggested), followed by a Gröb type of fragmentation.[23]



Loganin
12

6

(6)

This concept of secologanin formation has been challenged by Inouye, who has fed 10-hydroxyloganin to plants and does not feel that the low incorporation of this into 9, which he obtained, validates the theory presented in eq. 6.[102]

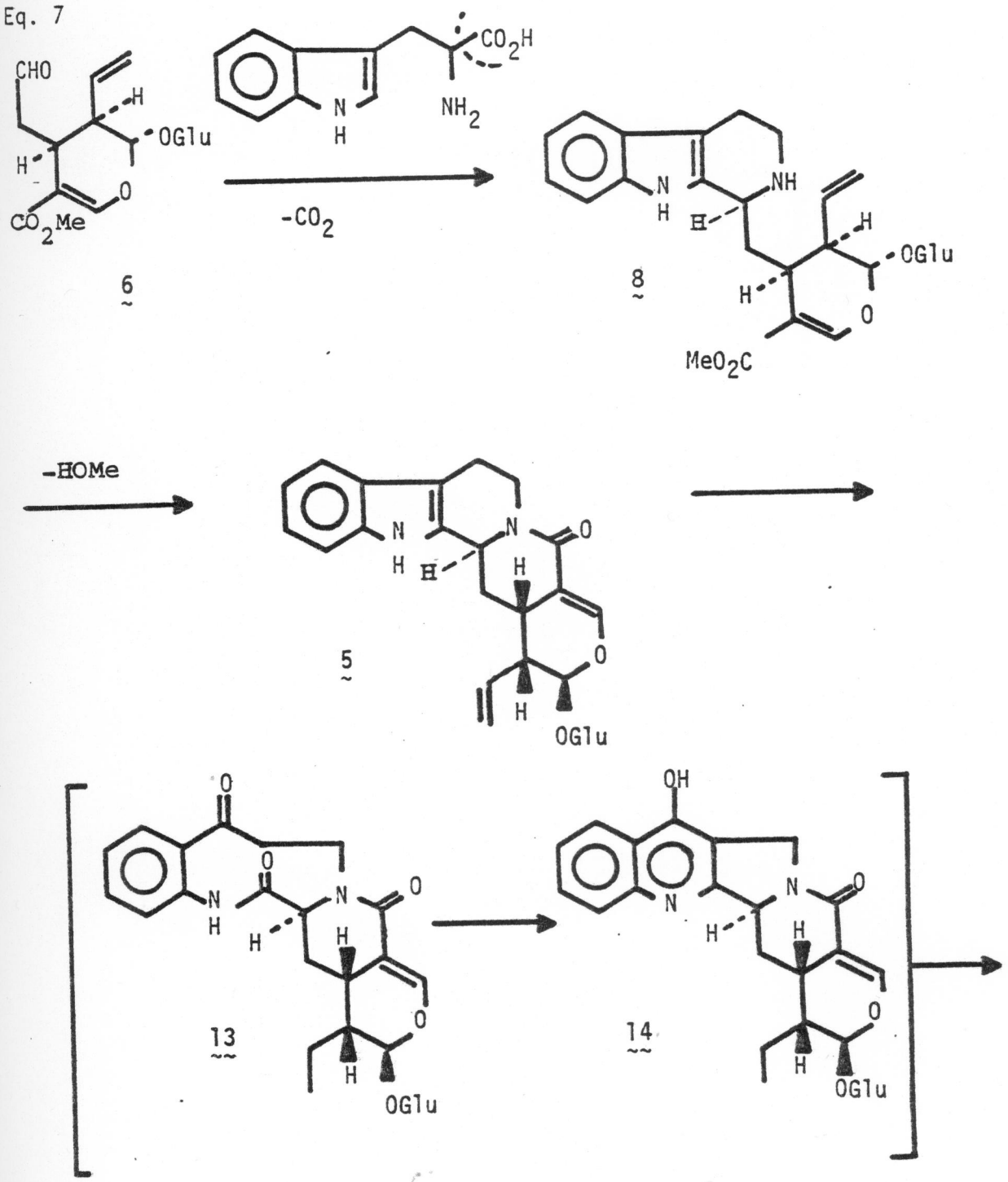
C. Camptothecin Biosynthesis

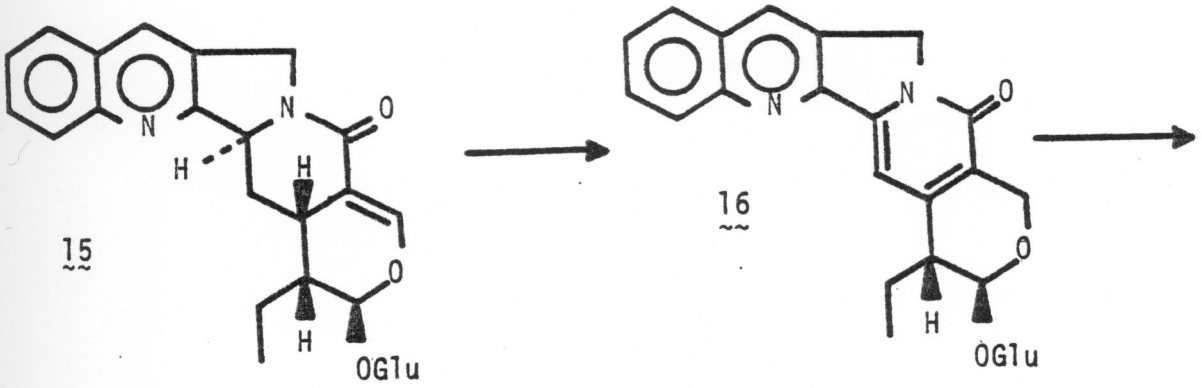
Although all of the biosynthetic intermediates leading to camptothecin are not known, enough have been characterized so that chemical analogies can be made and a reasonable hypothesis developed for its formation. Heckendorf, et al. have shown that labelled mevalonate and tryptophan are precursors of camptothecin in plant tissues.[53] Formation of the alkaloid starts with a Mannich condensation between tryptamine and secologanin, giving strictosidine (8). It is believed that expansion of the B-ring to form the quinoline skeleton occurs by the oxidative cleavage illustrated (13 to 14, eq. 7). An aldol condensation, followed by loss of the C-2 hydroxyl may give compound 15, which could be appropriately modified to yield camptothecin.

D. Biomimetic Synthesis of Camptothecin

An early attempt at construction of the camptothecin's basic heterocyclic framework was reported by Wenkert in 1967.[28] Wenkert considered his synthetic approach to be a biomimetic one (eq. 8) because he felt that isositsirikine (18) could be converted to camptothecin by analogous in vivo reactions.[25-27] This presupposed that the indole to quinoline conversion occurred at an early stage, i.e., he proposed that the oxidative ring conversion was accomplished shortly after the initial Mannich condensation of tryptamine and an unspecified terpene (eq. 8).[28,29] Lactone and pyridone ring formation were thought to be later biosynthetic events.

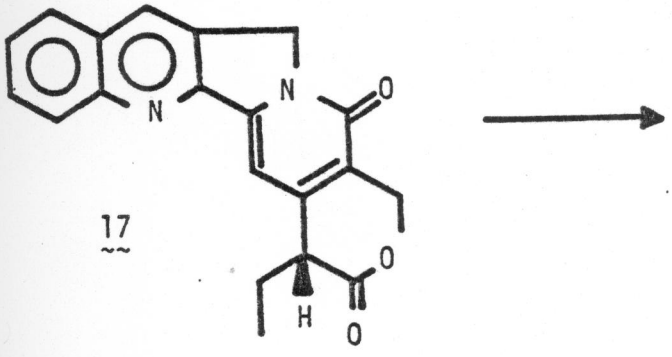
Eq. 7


CHO
H
OGlu
H
O
CO2Me
CO2H
NH2
N
H
-CO2
6
8
NH
H
MeO2C
-HOMe
5
OGlu
13
14
OH



15

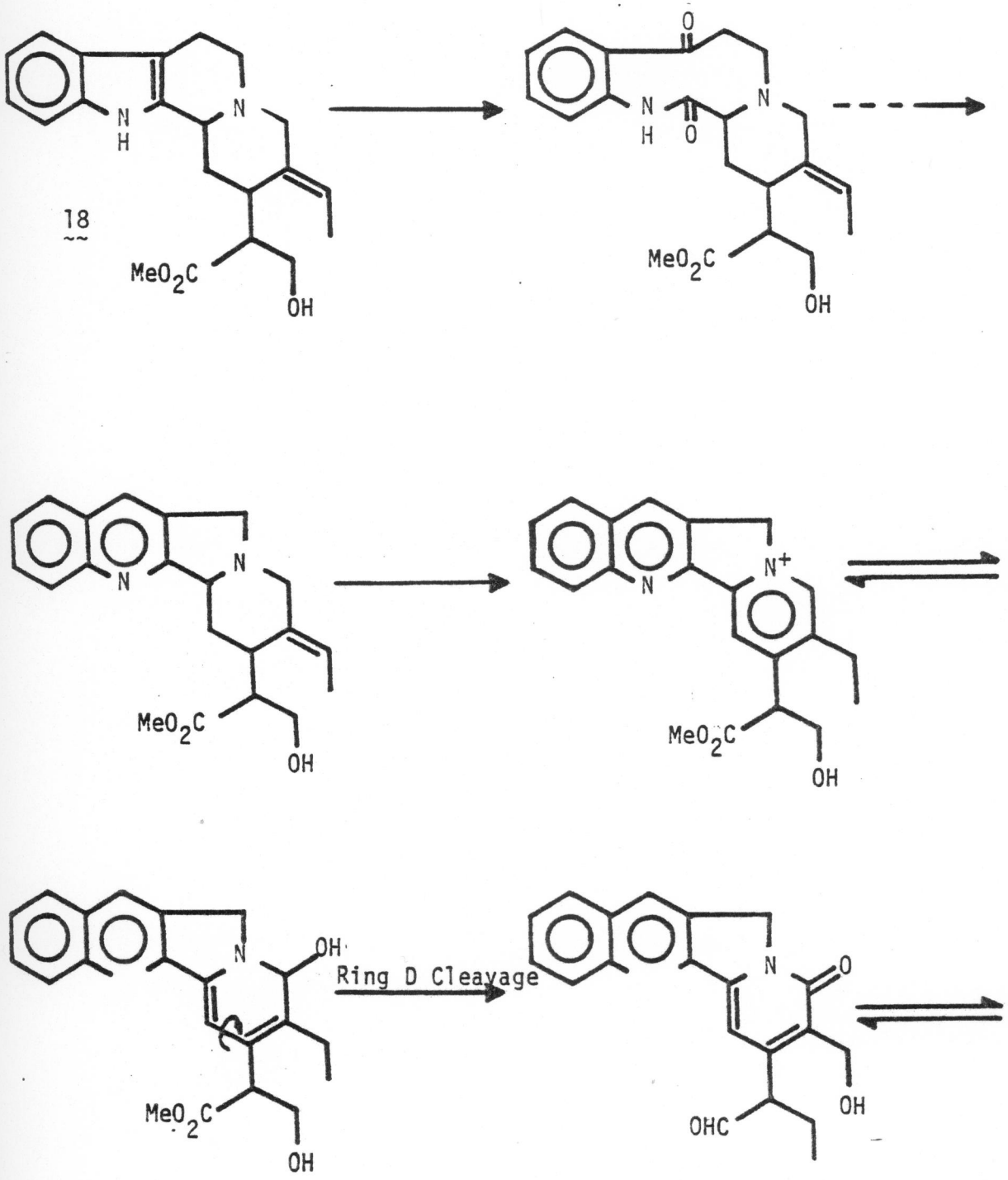
16

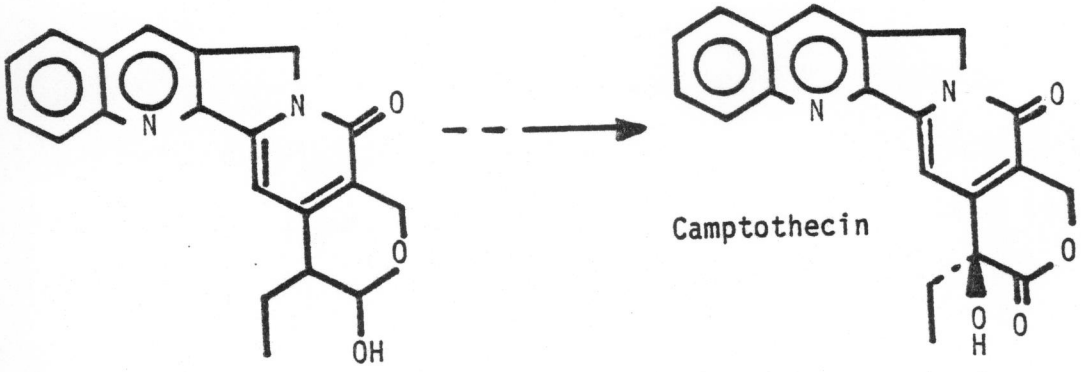


17

1

Eq. 8



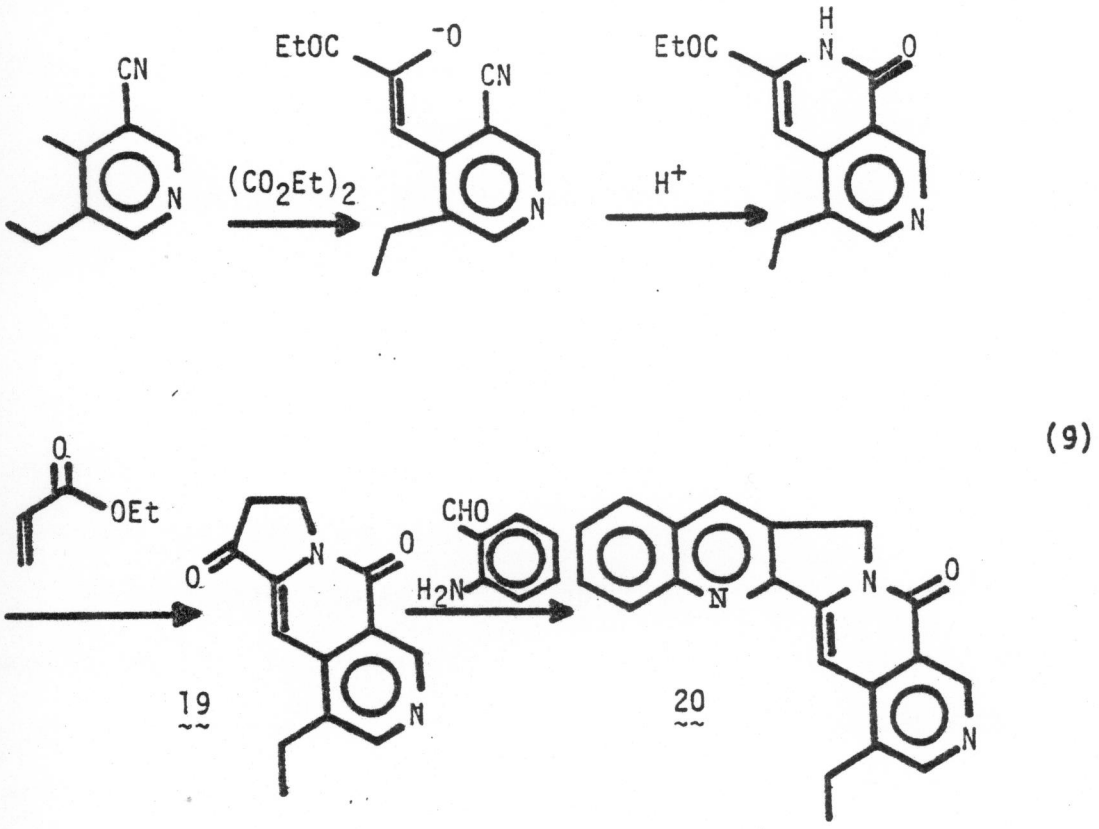


Camptothecin

Wenkert's construction of the camptothecin framework was a model study rather than a synthetic attempt because his product, 20, was a ring-E pyridine as opposed to the naturally occurring ring-E δ-lactone of 1. In his reaction sequence (eq. 9), 4-methyl-5-ethylnicotinonitrile was condensed with diethyl oxalate to form an enolate that cyclized to a lactam upon treatment with mild acid. Condensation with ethyl acrylate gave a keto-ester which was decarboxylated to form a five-membered, cyclic ketone, 19. This ketone was converted to the camptothecin model, 20, by a Friedlander quinoline synthesis (eq. 9).

Recent data have shown that in the biogenesis of camptothecin, lactol and lactam formation occur before the indole-to-quinoline conversion. This is based upon the prior results of other workers which showed that strictosidine (8) is a key intermediate of many indole alkaloids which utilize tryptamine and secologanin as their precursors.[31-34]

Feeding experiments with isotopically labelled strictosamide (9) and strictosidine have shown that the indole to quinoline rearrangement happens near the end of the biosynthetic sequence to camptothecin. Labelling studies with the quinolol analog (14, eq. 7) were done to rule out the possiblity that strictosamide is oxidized directly to its quinolol intermediate, 14, before ring-D oxidation, but the results were negative.[53] Additional insight about the subsequent steps of the biosynthetic pathway has not been



(9)

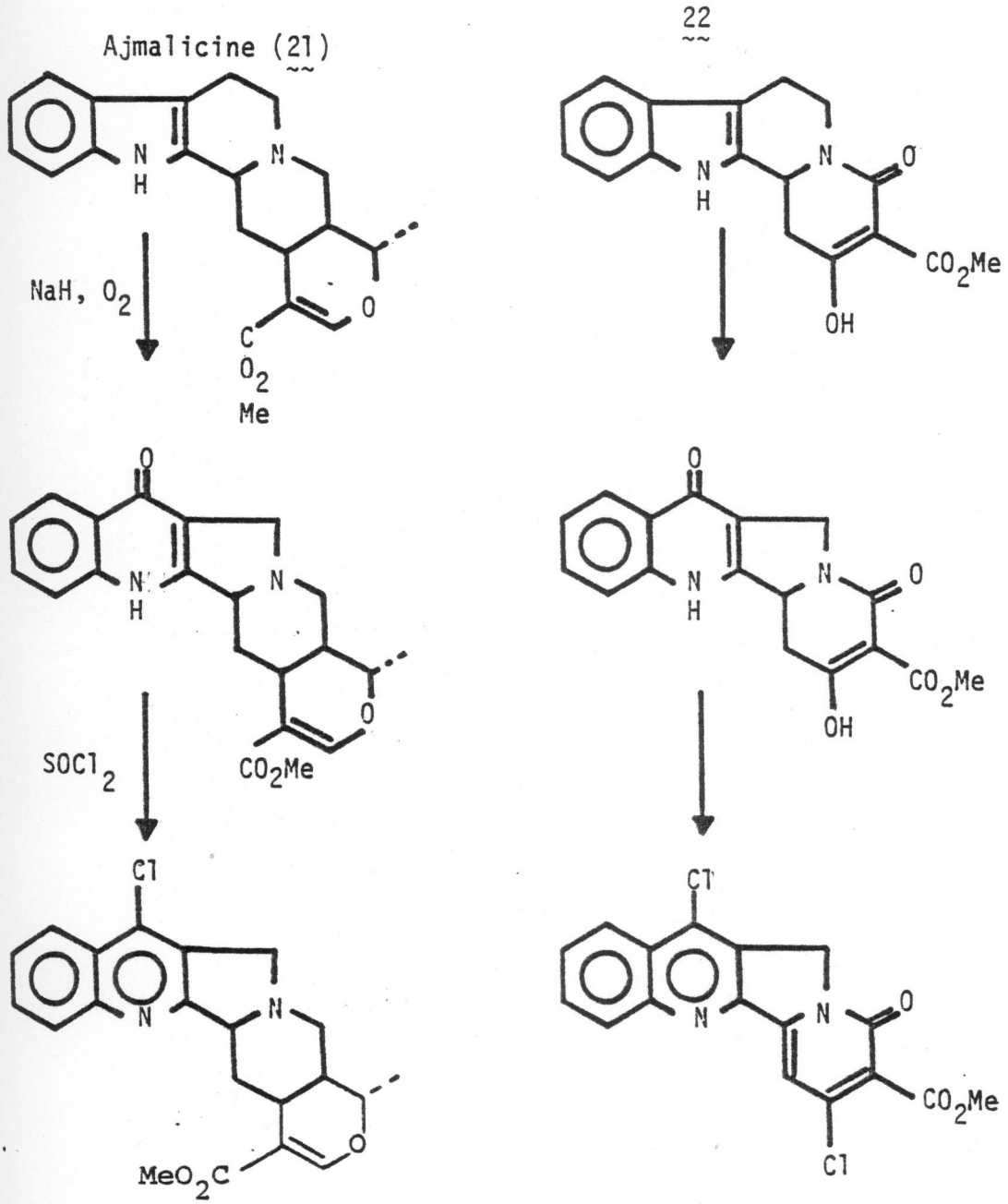
obtained. Whatever the exact details, it seems reasonable to conclude that the B-ring expansion takes place at a very late stage in the biosynthetic pathway, and that the formation of the lactam takes place at mid-stage.[27,28]

In light of the above discussion, it is obvious that any total synthesis of camptothecin must involve a condensation of tryptamine and secologanin (or a synthetic equivalent) to be considered biomimetic either in a sequential or a constructional sense.

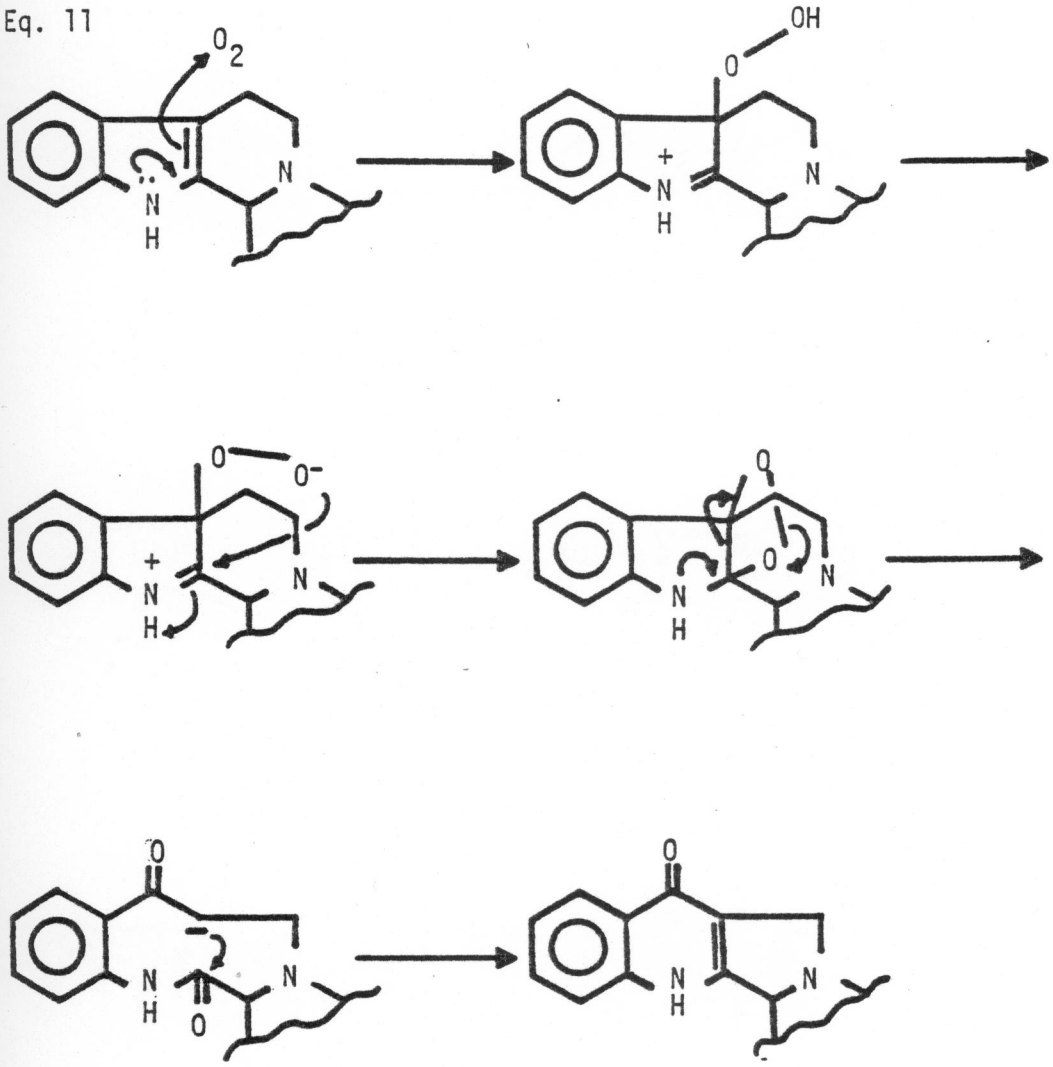
Winterfeldt, in some model studies aimed at a biomimetic synthesis of camptothecin, investigated chemically induced ring B expansions in ajmalicine (21, eq. 10) and the lactam model 22.[28B,39] He found that the desired transformation was easily accomplished by oxidation (dimethylformamide, O_2 and KOtBu), followed by treatment with thionyl chloride. The mechanism for this sequence is felt to involve the following steps (eq. 11, 12).

Winterfeldt's synthesis of camptothecin, which was biomimetic only in the ring interconversion, is depicted in eq. 13. In this synthesis, the indole starting material, 23, was acylated with malonic semi-ester Cl and underwent intramolecular cyclization to form the keto-lactam, 25. This compound was converted to the corresponding methyl-enol ether, 26, with diazomethane. Michael addition of tertiary-butyl malonate, followed by elimination of methoxide, led to the lactam-triester, 27. The latter compound was then converted to quinoline 28 by the oxidative procedure shown earlier. The resultant quinoline compound was dehydrogenated with thionyl chloride to give the halo-pyridone, 29, in good yield. After the dehydrogenation, the halo-pyridone was dehalogenated by hydrogenation with a palladium catalyst on a barium sulfate support. Selective reduction

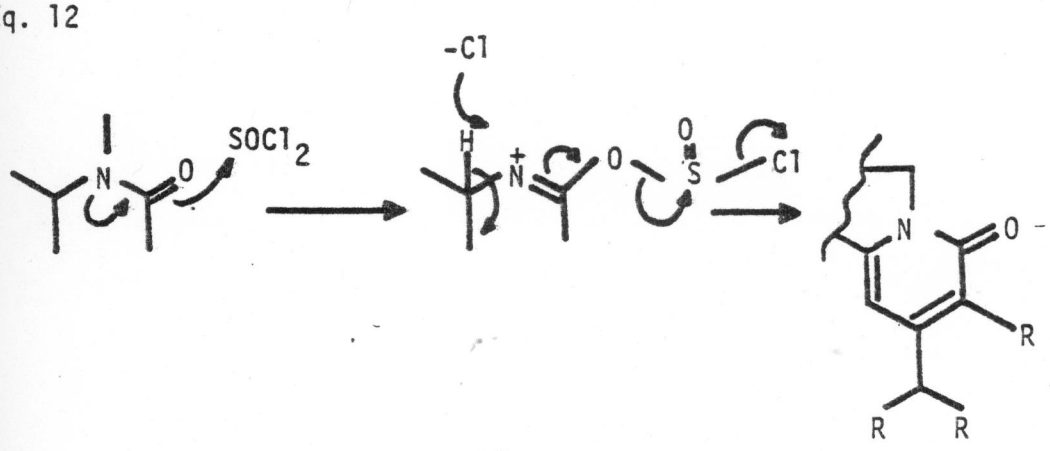
Eq. 10



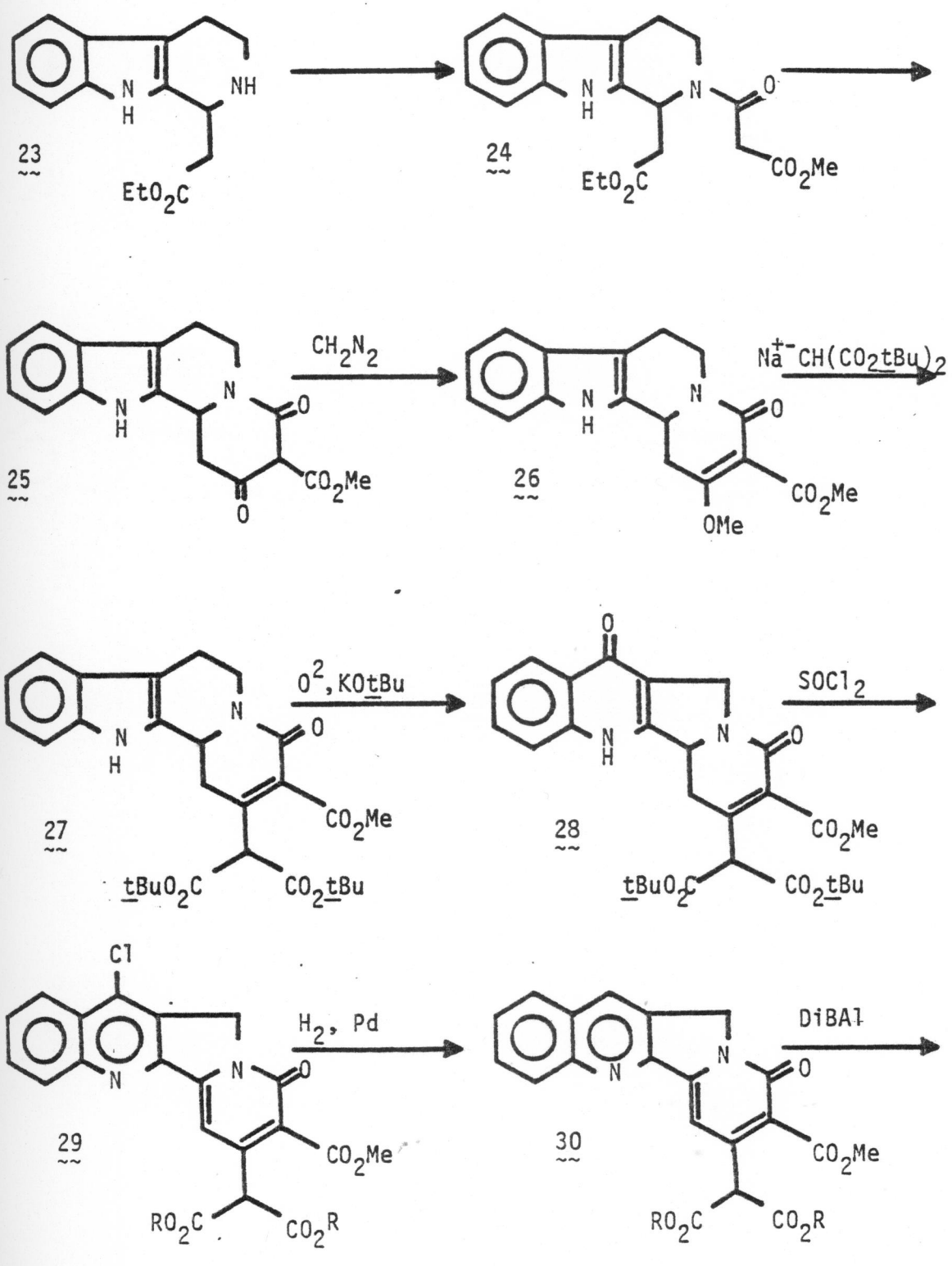
Eq. 11

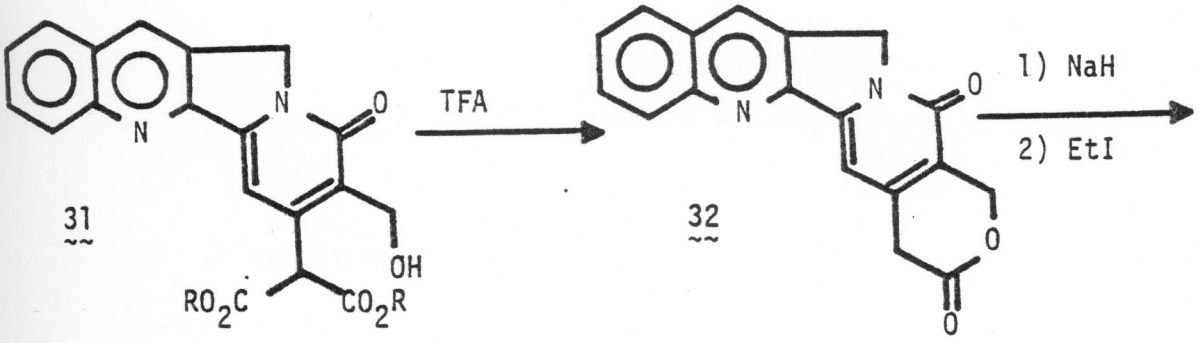


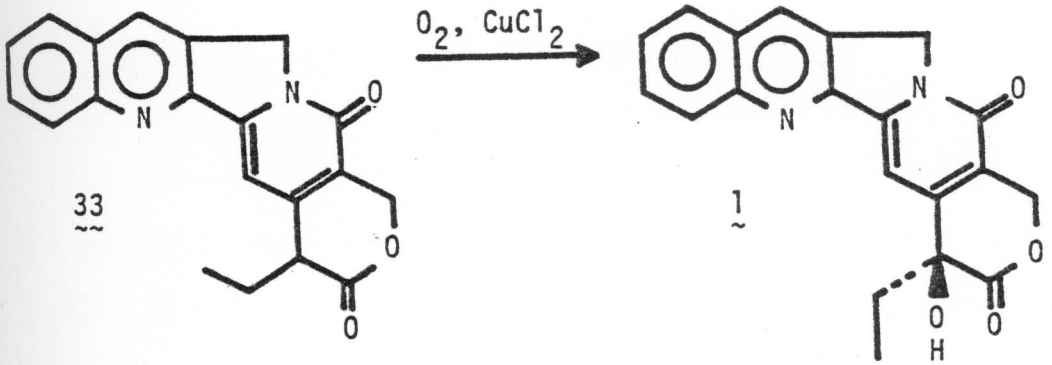
Eq. 12



Eq. 13


23
24
25
26
27
28
29
30
CH_2N_2
$Na^{+-}CH(CO_2tBu)_2$
O^2, KOtBu
$SOCl_2$
H_2, Pd
DiBAl
EtO_2C
CO_2Me
OMe
$tBuO_2C$
CO_2tBu
RO_2C
CO_2R
Cl


TFA
1) NaH
2) EtI
31
32
OH
RO_2C
CO_2R
N
O

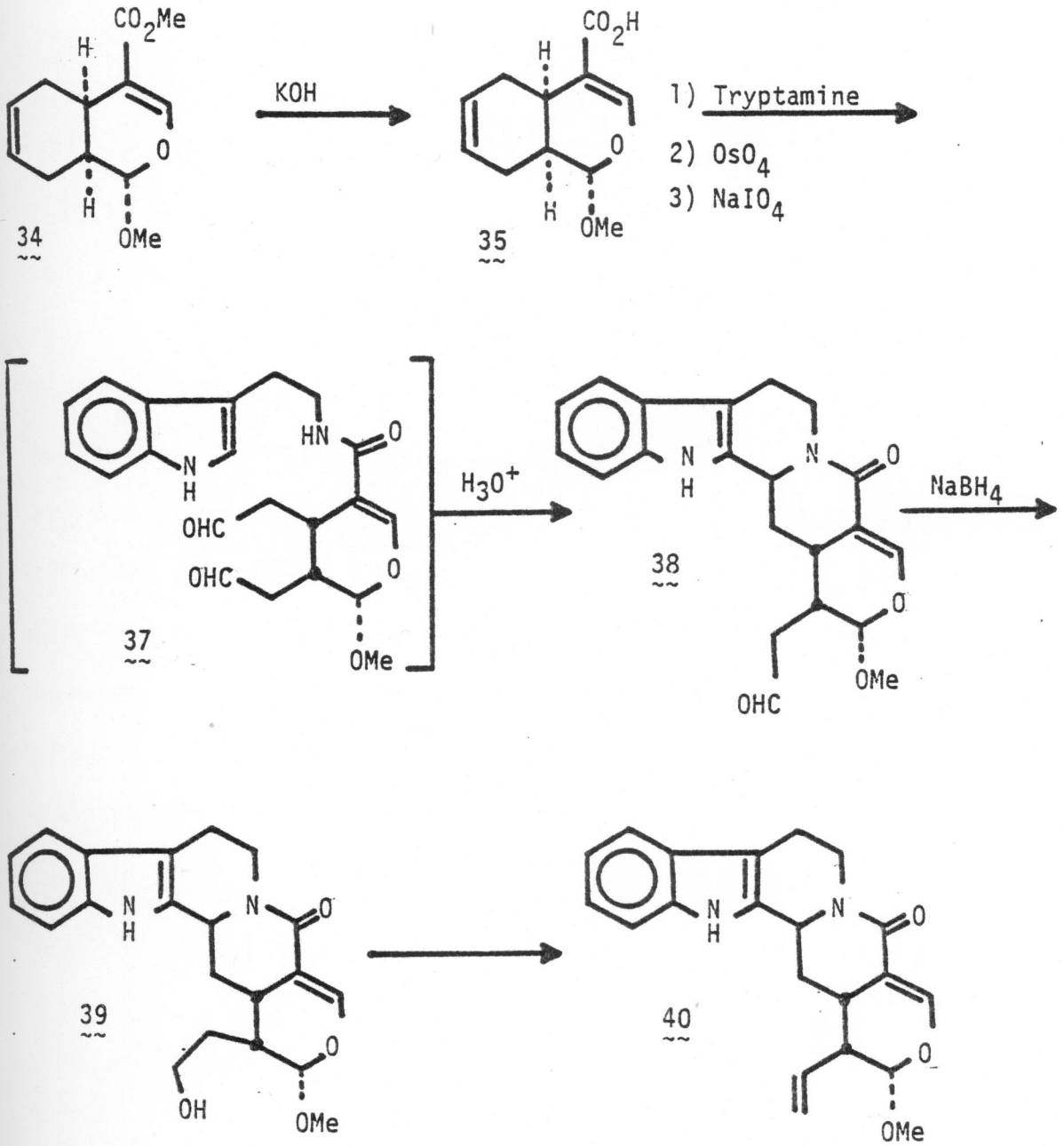

O_2, $CuCl_2$
33
1
N
O
H

of the methyl ester of 30 was accomplished with diisobutylaluminum hydride. Reduction with sodium borohydride gave carbinol 31, which was transformed into a lactone (32) upon treatment with trifluoroacetic acid. The lactone was alkylated by treatment with sodium hydride followed by ethyl iodide. Introduction of the tertiary hydroxyl group was effected by aeration of the deoxy compound, 33, in dimethylformamide (containing a trace of aliphatic amine), in the presence of copper (II) ions. This gave camptothecin in about 6% overall yield from 23.

E. Biomimetic Strategy of Hutchinson et al.

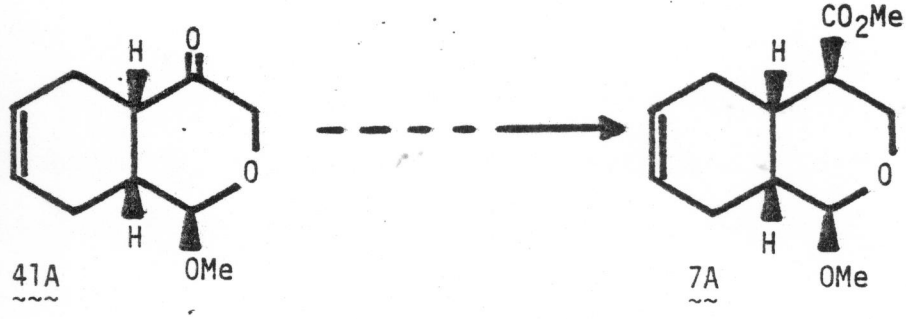
The biomimetic synthesis of camptothecin that we are developing has a general strategy that involves condensation of tryptamine with a synthetic equivalent of secologanin. As an example of our general plan, Knutson has achieved the synthesis of 18, 19-dihydro-1-O-methyl strictosamide (40) by the method depicted in eq. 14.[15,55] In this preparation, the methyl ester of the 2-oxa-decalin, 34, was converted to its corresponding carboxylic acid and condensed with tryptamine, via active ester coupling procedures, to yield a secondary amide. Selective cleavage of the isolated doubled bond was achieved through the use of a catalytic amount of osmium tetroxide and N-methyl morpholine-N-oxide, followed by vicinal diol cleavage using sodium periodate. This gave dialdehyde 37, which underwent acid catalyzed Mannich condensation to form the C-18 aldehyde of 1-O-methyl strictosamide, 38, and its C-3 epimer. Sodium borohydride

Eq. 14


CO2Me
H
O
H
OMe
34
KOH
CO2H
H
O
H
OMe
35
1) Tryptamine
2) OsO4
3) NaIO4
HN
O
N
H
OHC
OHC
O
OMe
37
H3O+
N
H
N
O
O
OMe
OHC
38
NaBH4
N
H
N
O
O
OH
OMe
39
N
H
N
O
O
OMe
40

reduction of this C-18 aldehyde to a primary alcohol, 39, conversion to the primary alkyl bromide and then dehydrohalogenation gave the desired olefin, 40. Subsequent steps that would lead from 40 to camptothecin have not yet been accomplished, but are not anticipated to present an obstacle.[6,7,15]

A methodology for the development of a biomimetic route to C-16,17 unsaturated strictosamide analogs is desired because it would give us compounds needed for biosynthetic experiments and derivatives of camptothecin for studies of its mechanism of action. The plan which was chosen is very similar to that shown in eq. 14 except that the 2-oxa-decalin synthon is saturated at the C-3,4 position. Synthesis of this ester, 7A (eq. 15), relied upon an efficient preparation of the cis-2-oxa-4-decalone, 41A, by a Diels-Alder reaction. The synthesis and characterization of 7A was my research goal. Accordingly, the main direction that this thesis takes is to develop the synthesis and possible uses for this and analogous iridoid synthetic intermediates.

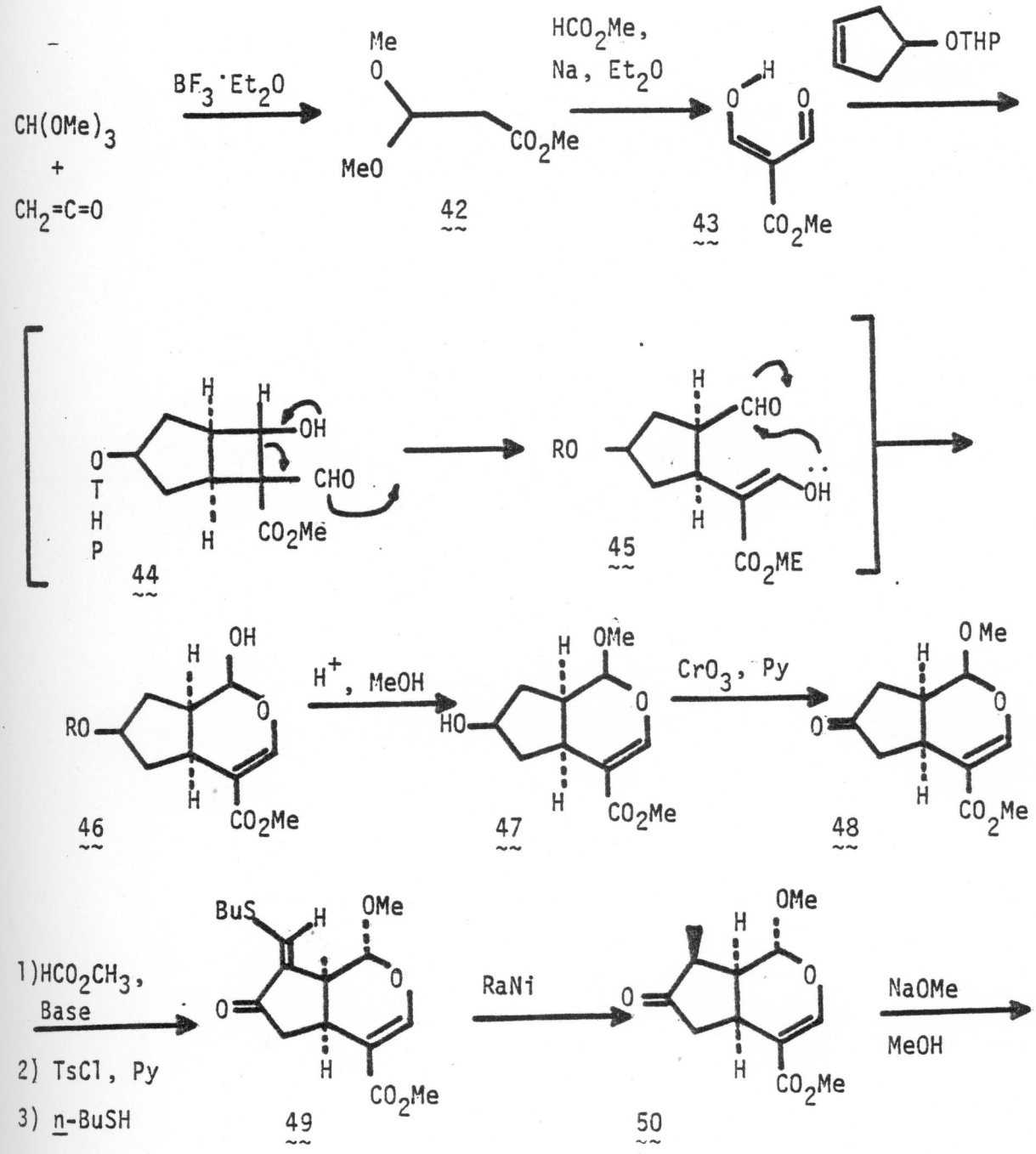


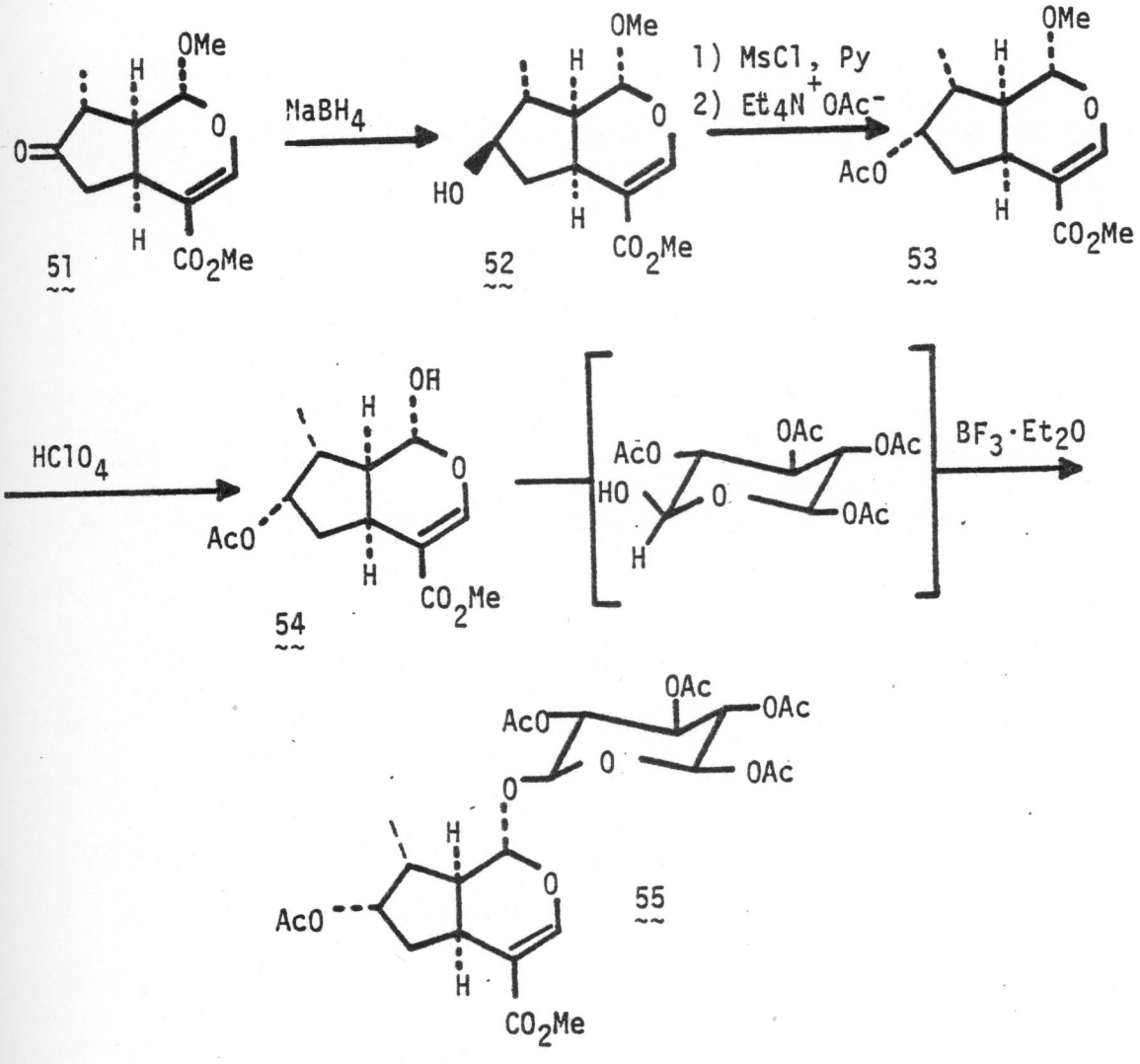
(15)

F. Synthetic Chemistry of Cyclopentanomonoterpenoids

The first total synthesis of loganin pentaacetate, achieved by Büchi, utilized deMayo's enone-photoannulation procedure to form the iridoid framework in one step (eq. 16).[56-59] Condensation of ketene and trimethyl orthoformate, catalyzed by boron trifuoride etherate, formed the β-dimethyl acetal, methyl ester 42 which was formylated by methyl formate to afford methyl diformylacetate, 43. A [2+2] photochemical cycloaddition between 3-cyclopentene-1-O-tetrahydropyranyl ether and 43 gave, initially, bicyclo-[3.2.0]-heptene 44, which underwent a retro-aldol condensation to form a 1,5-dialdehyde, 45, which recyclized to the desired tetrahydro-coumalate ester, 46. The 2-oxa-bicyclo-[3.4.0]-nonene was converted to its 1-O-methyl acetal upon treatment with acidic methanol, which also resulted in cleavage of the tetrahydropyranyl protecting group. Oxidation of secondary alcohol 48, followed by a non-regioselective sequence of C-8 formylation, conversion of the formyl group to its corresponding n-butylthiomethylene derivative and reductive de-sulfurization, gave 50 in good overall yield.[60] The resulting cis, C-8 methyl group was epimerized with sodium methoxide and the ketone, 51, then converted to carbinol 52 by borohydride reduction. Mesylation of this carbinol and S_N2 displacement by acetate gave the C-7 acetate, 52, with the correct relative stereochemistry. De-protection of the C-1 oxygen followed by glucosidation to form (-)-loganin pentaacetate, 55, was accomplished by the method of

Eq. 16


CH(OMe)3
+
CH2=C=O
BF3·Et2O
Me
O
MeO
CO2Me
42
HCO2Me,
Na, Et2O
H
O
O
CO2Me
43
OTHP
OH
CHO
CO2Me
OTHP
44
RO
CHO
OH
CO2ME
45
OH
RO
CO2Me
46
H+, MeOH
OMe
HO
CO2Me
47
CrO3, Py
O Me
O
CO2Me
48
1)HCO2CH3,
Base
2) TsCl, Py
3) n-BuSH
BuS
OMe
CO2Me
49
RaNi
OMe
CO2Me
50
NaOMe
MeOH

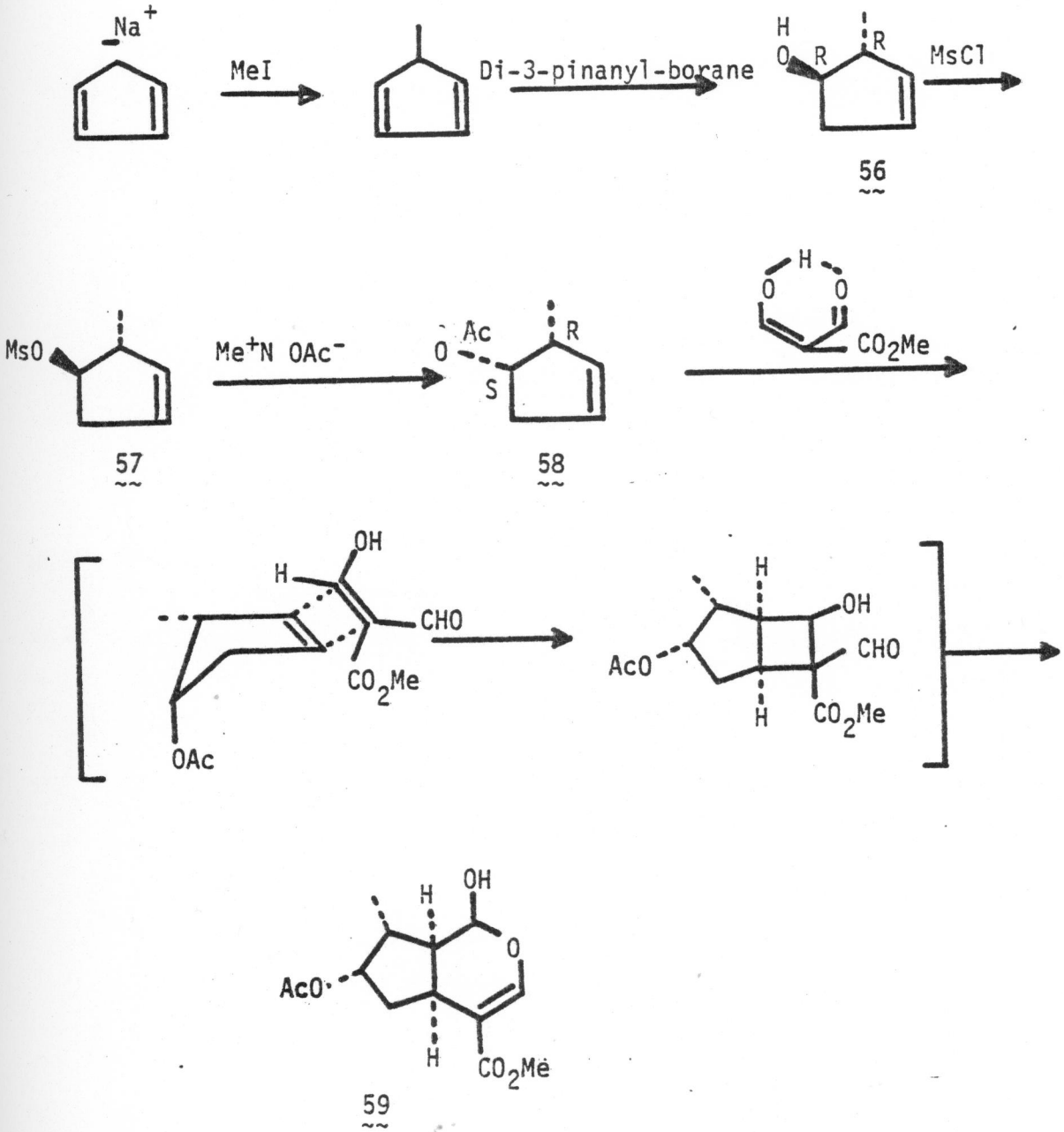

OMe
H
O
O
H
CO2Me
51
NaBH4
HO
52
1) MsCl, Py
2) Et4N+ OAc-
AcO
53
HClO4
OH
54
AcO
OAc
BF3·Et2O
55

Sandoz, but in very poor yield (1.4% from 53).[61,62]

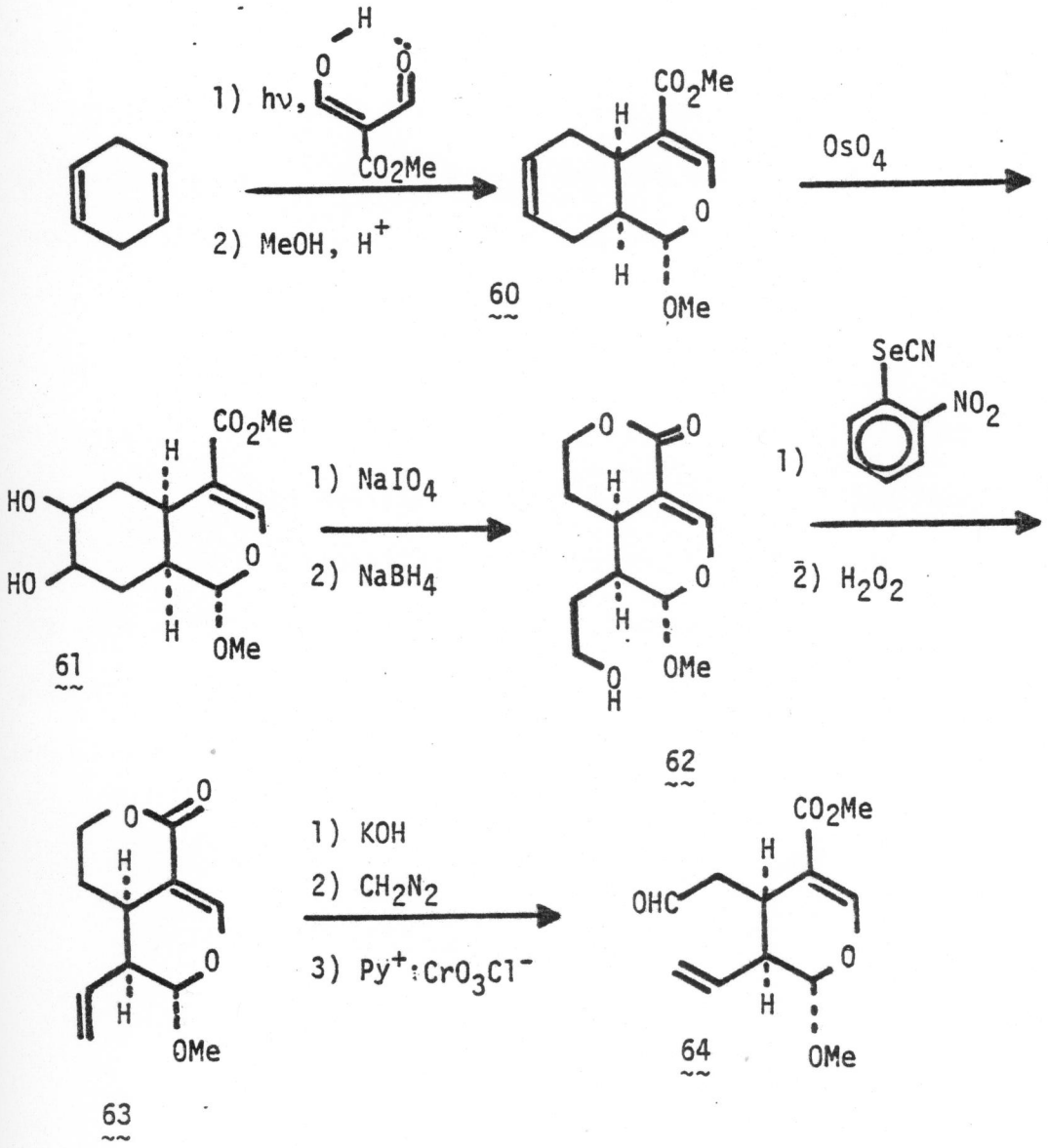
A much simpler and enantioselective procedure for preparation of loganin aglucone (59) was performed by workers at Hoffmann-La Roche (eq. 17).[63] 5-Methyl cyclopentadiene was hydroborated with di-3-pinanylborane to give the chiral cyclopentenol (56) in 30% yield. Mesylation of the secondary alcohol, followed by S_N2 displacement with acetate anion produced the desired chirality in the resulting cyclopentene, 58. Photoannulation with methyl diformylacetate, 43, led to a partially stereoselective formation of 7-O-Ac loganin aglucone, 59, in 22% yield.[64,65]

Research of our group, in collaboration with Hoffman-LaRoche, led to a simple and stereoselective preparation of (±)-secologanin aglucone-O-methyl ether (64, eq. 18).[55] Photochemically induced [2+2] cycloaddition of cyclohexadiene and methyl diformylacetate gave 2-oxa-decalin 60 in 62% yield. This was converted to the C-7,8 vicinal diol, 61, with osmium tetroxide (catalytic amount) and N-methyl morpholine N-oxide. Sodium periodate cleaved the diol and the resultant aldehyde groups were reduced to primary alcohols by sodium borohydride. At this point, the ester and the C-7 carbinol cyclized *in situ* to form the unsaturated δ-lactone, 62. Conversion of the C-8 alcohol to the olefin was accomplished with o-nitrophenyl selenocyanate, followed by treatment with hydrogen peroxide. Basic hydrolysis of lactone 63, esterification of the carboxylic acid thus formed, and oxidation of the C-7 primary alcohol yielded secolo-

Eq. 17


Na+
MeI
Di-3-pinanyl-borane
H
O
R
R
MsCl
56
MsO
Me+N OAc−
Ac
O
S
R
57
58
H
O
O
CO2Me
OH
H
CHO
CO2Me
OAc
H
OH
AcO
CHO
H
CO2Me
OH
H
O
AcO
H
CO2Me
59

Eq. 18


1) hν,
CO2Me
2) MeOH, H+
60
OsO4
CO2Me
HO
HO
OMe
61
1) NaIO4
2) NaBH4
SeCN
NO2
1)
2) H2O2
OMe
62
1) KOH
2) CH2N2
3) Py+:CrO3Cl−
OHC
CO2Me
OMe
63
64

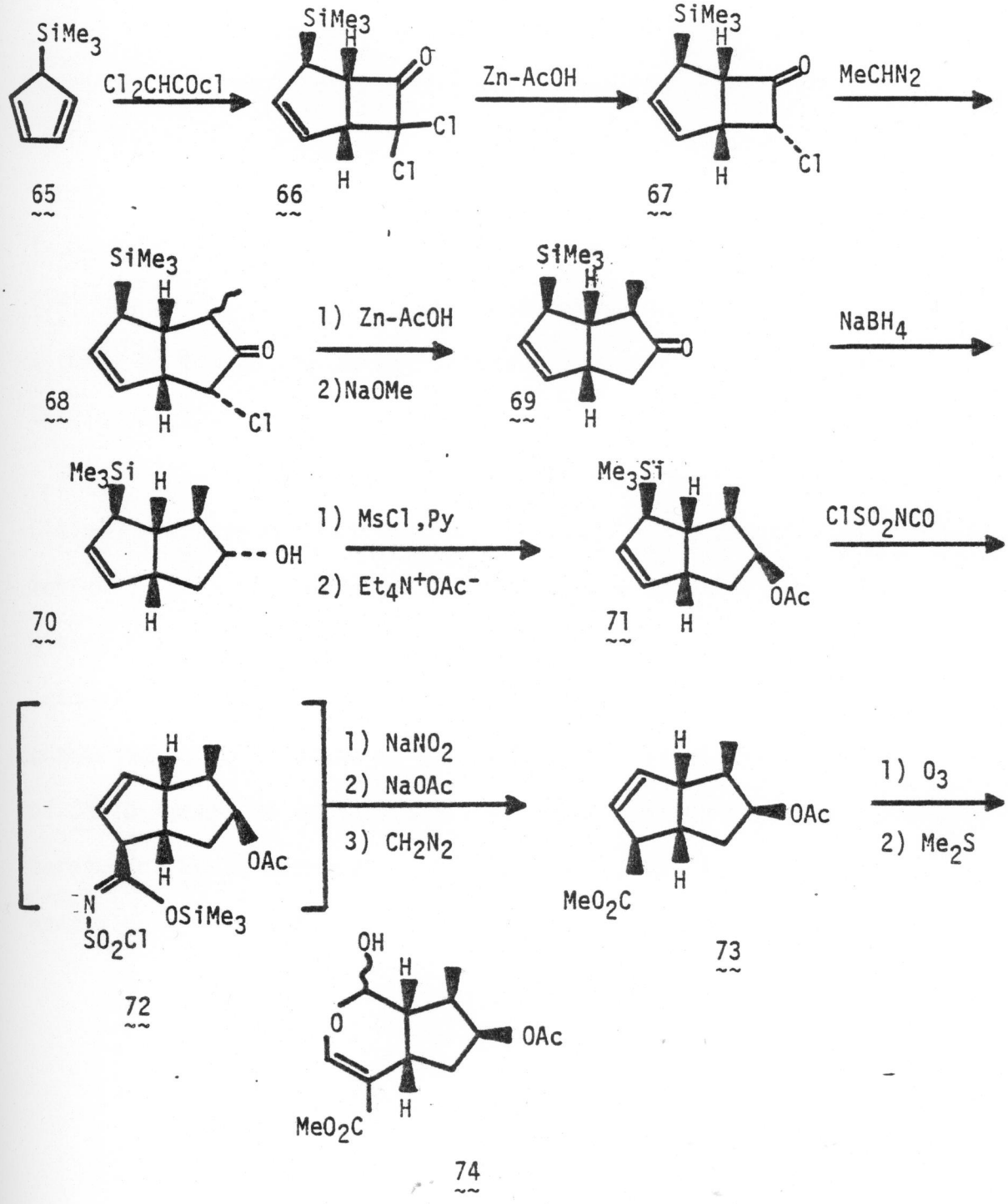
ganin aglucone-O-methyl ether, 64, in 22% overall yield from cyclohexadiene and methyl diformylacetate.

A novel approach to racemic loganin aglucone acetate, 74, by Fleming, et al., utilized the reaction of allylsilanes with electrophiles (eq. 19).[66,67] Thus, the [3.2.0] bicycloheptanone, 66, was monodechlorinated with zinc/acetic acid and reacted with diazomethane to give cyclopentanone 68 by ring expansion (eq. 20). This ketone was dechlorinated and then reduced to the secondary carbinol by sodium borohydride. Mesylation of 70, followed by an S_N2 displacement with acetate anion developed the appropriate stereochemistry in compound 71. Conversion of the allyl silane in 72 to the methyl ester, 73, was accomplished through the use of chlorosulphonyl isocyanate as an electrophile. A subsequent hydrolysis of 73 afforded the acid which was then esterified. Double-bond ozonolysis and cyclization of the dialdehyde gave aglucone 74 in 5.3% overall yield from cyclopentadiene.

(19)

Whitesell's synthesis of sarracenin is worth mentioning here because it created a synthon, 82, known to be intraconvertible to the six-membered lactols characteristic of secoiridoids.[103]

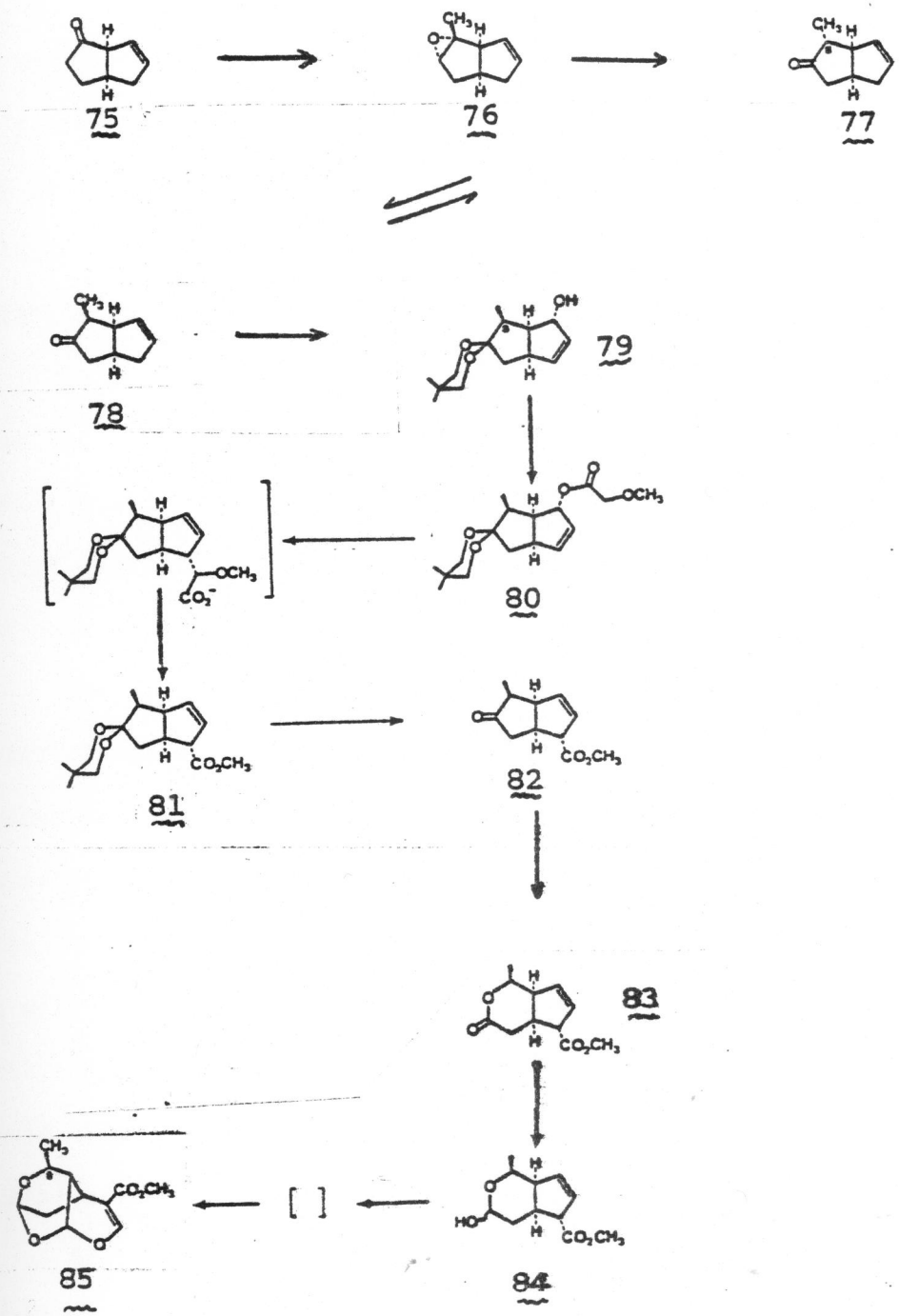
Eq. 20


SiMe3
Cl2CHCOCl
Zn-AcOH
MeCHN2
Cl
H
O
65
66
67
1) Zn-AcOH
2)NaOMe
NaBH4
68
69
Me3Si
OH
1) MsCl,Py
2) Et4N+OAc-
ClSO2NCO
OAc
70
71
1) NaNO2
2) NaOAc
3) CH2N2
OSiMe3
SO2Cl
72
1) O3
2) Me2S
MeO2C
73
74

In this work (eq. 21), the bicyclic ketone, 75, was converted to epoxide 76 by successive treatment with methyl lithium, aqueous acid, and m-chloroperoxybenzoic acid.[104] The bicyclic epoxide rearranged to form a methyl ketone, 77, upon treatment with boron trifluoride etherate. This ketone, with the wrong C-8 stereochemistry, was epimerized by sodium methoxide, and the correct isomer, 78, separated by liquid chromatography (HPLC). The ketone (78) was then protected and the double-bond converted to an allylic alcohol by the action of m-chloroperoxybenzoic acid, followed by lithium diethyl amine.

The new carbon-carbon bond of 81 was formed by an ester-enolate Claisen rearrangement of α-methoxyacetate, 80. Oxidative decarboxylation of the α-methoxycarboxylic acid removed the extra carbon, giving the desired methyl ester, 81. Deprotection of the ketone was accomplished by exposure to aqueous acid to give 82, which was then converted to a δ-lactone by Baeyer-Villiger oxidation. Reduction of 83 to lactol 84 by diisobutyl aluminum hydride permitted conversion of 84 to sarracenin (85) by ozonolysis, followed by treatment with zinc/acetic acid.

Eq. 21



III. Development of a 3,4-Dihydrosecologanin Equivalent

A. Historical

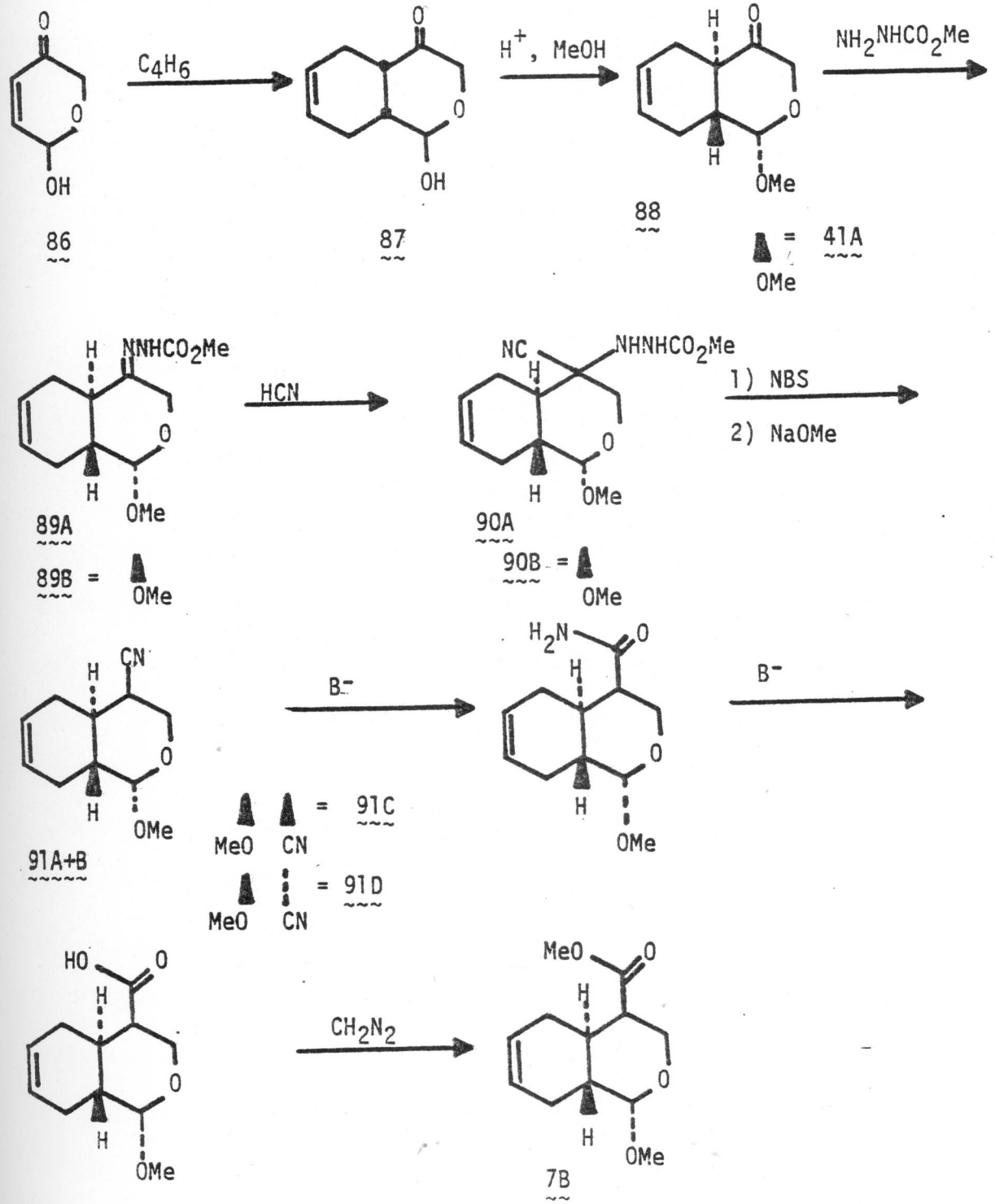
It had been demonstrated in 1974 by Jones that 5,6-dihydropyran-3-one-6-ol, (86, eq. 22), underwent the Diels-Alder reaction to yield a 2-oxa-4-decalone, 87. This adduct was then converted to the corresponding C-1-O-methyl acetal by treatment with acidic methanol. The bridgehead stereochemistry of 88 was reportedly cis, although this was not well substantiated by Jones.[71]

To prepare the desired methyl ester (7A from the ketone synthesized by Jones (88), Drs. Hsia and Mattes had developed a synthetic route which involved conversion of the ketone to the homologous nitrile, 91, hydrolysis to its carboxylic acid and esterification with diazomethane (eq. 22).

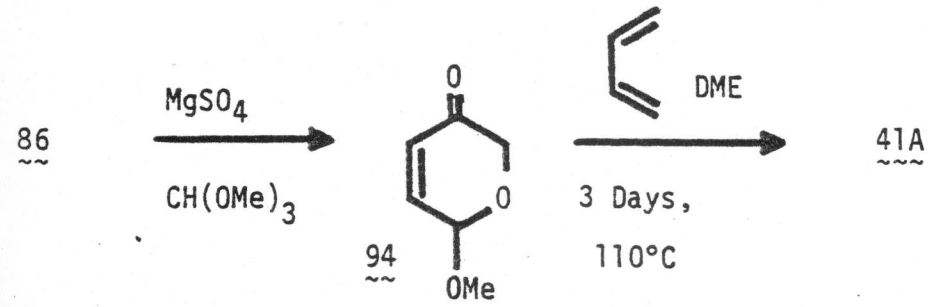
When I began my research we wished to develop a method to methylate dihydropyrone 86 before the Diels-Alder reaction. This seemed desirable because the other researchers had had some trouble obtaining clean, C-1 acetalated 88 by Jones' method. It is assumed that they were getting side reactions involving C-4 ketal formation, as well as the observed formation of an epimeric mixture of C-1 methyl acetals. Therefore, it was felt that an alternate approach would lead to a single, stereochemically defined bicyclic ketone-acetal, 41A.

Acetalization of the C-1 hemiacetal, 86, by the method of Torii, et al., gave us the desired compound (94) as anticipated,

Eq. 22.


C4H6
H+, MeOH
NH2NHCO2Me
86
87
88
41A
HCN
89A
89B
90A
90B
1) NBS
2) NaOMe
B-
91A+B
91C
91D
MeO
CN
CH2N2
7B

although in moderate (about 40-50%) yield. This C-1 acetal underwent the thermal Diels-Alder reaction to give us a much cleaner product then had been obtained previously by Mattes and Hsia (eq. 23).[72]



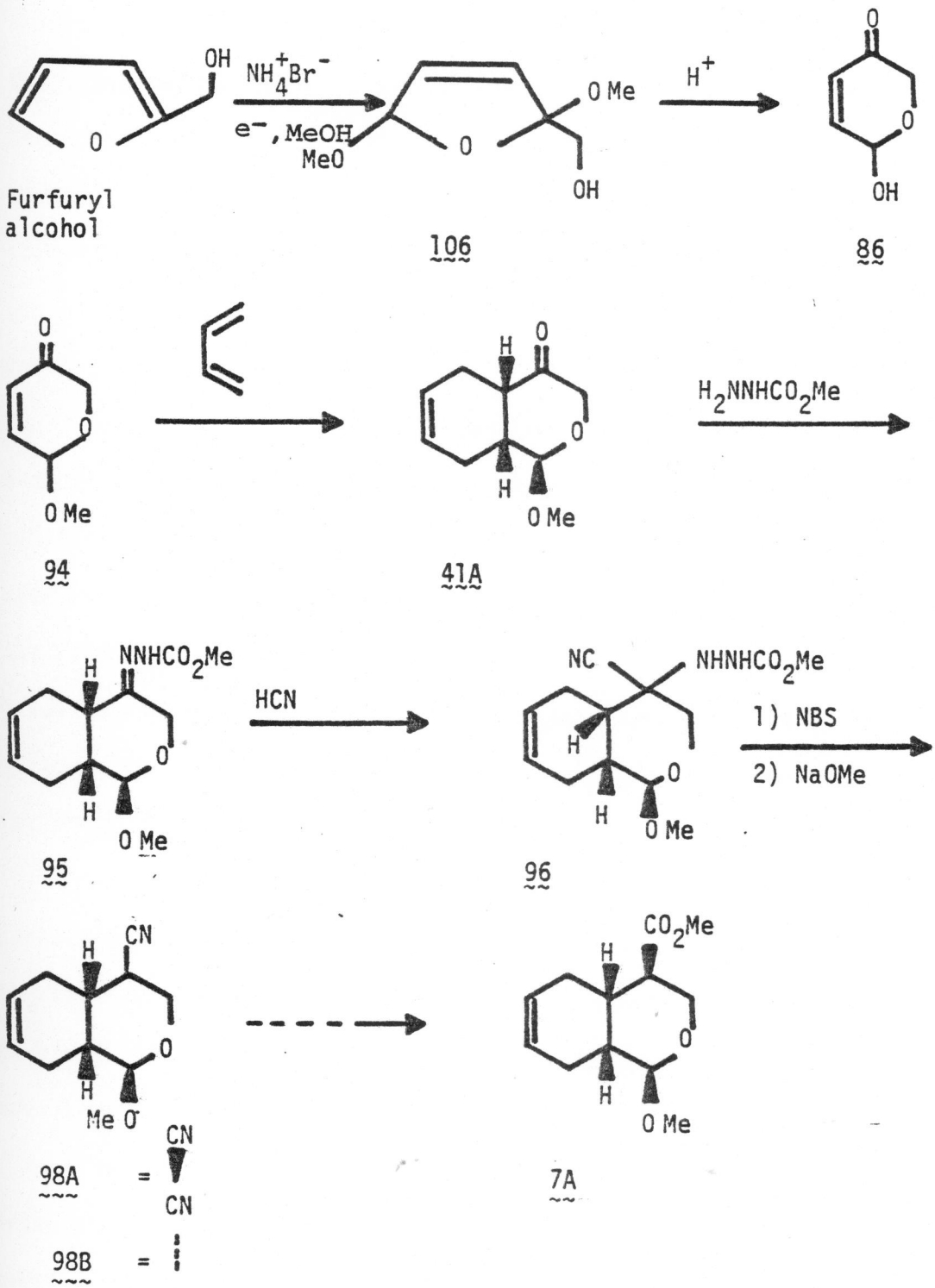
(23)

Because my co-workers had completed the synthesis of 3,4-dihydrosecologanin equivalent 7B prior to my improved preparation of the ketone-acetal, we decided to publish our synthesis at this time (eq. 24).[12] Later as a means of checking our work, I attempted to carry the 2-oxa-4-decalone (41A), prepared by my method, through the rest of the published synthesis. It was at this point that discrepancies became apparent between my results and those of Drs. Mattes and Hsia.

B. Discussion

Our first indication that something unusual was happening came from the thin layer chromatography of purified methyl semicarbazone 95 obtained *via* my preparation of bicyclic ketone 41A. The R_f of this material did not exactly match Dr. Hsia's material and

Eq. 24


OH
$NH_4^+Br^-$
e^-, MeOH
MeO
O Me
OH
H^+
O
O
OH
Furfuryl alcohol
106
86
O
O
O Me
94
H
O
O
H
O Me
41A
H_2NNHCO_2Me
H
$NNHCO_2Me$
O
H
O Me
95
HCN
NC
$NHNHCO_2Me$
H
O
H
O Me
96
1) NBS
2) NaOMe
H
CN
O
H
Me O
98A = CN CN
98B =
H
CO_2Me
O
H
O Me
7A

recrystallized samples exhibited a second (lower R_f) spot when chromatographed. This second spot did not change in intensity despite repeated attempts at purification. At this time, this seemed to be a good indication of configurational equilibration; possibly of *syn* and *anti* conformers of the methyl semicarbazone.[73] This was consistent with the fact that the purified material (95) possessed a near-perfect elemental analysis, yet exhibited a wide range of melting points.

Convinced that my methyl semicarbazone was the desired material, I continued the synthetic sequence which we had published (eq. 24). Addition of cyanide should have led smoothly to the formation of the cyano-hydrazine, 96. Only with great difficulty was I able to make the reaction go, and it was capricious and low yielding at best. Oxidation of the cyano-hydrazine with *N*-bromosuccinimide gave a cyano-diazene, but this did not seem to undergo methoxide induced fragmentation to form the nitrile, 98.

As a result of the many discrepancies between the methyl semicarbazones prepared by two distinct methods (thin layer chromatographic mobilities, melting points, mixed melting points and chemical reactivity), we decided to examine the two compounds closely and ascertain their differences.

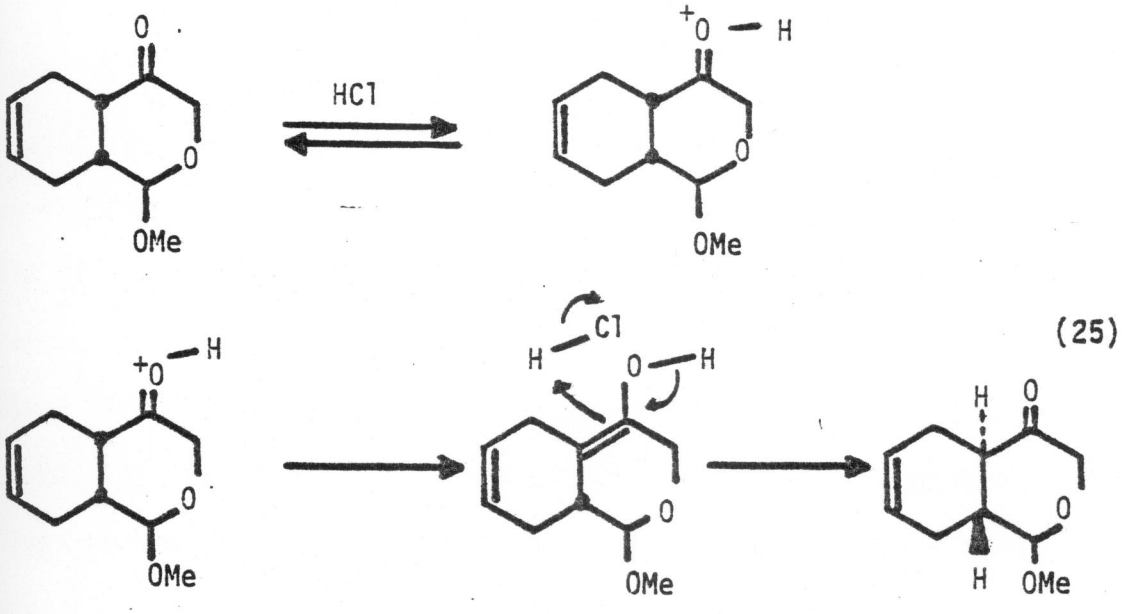
The two ketones, 41A and 88, were exposed to bridgehead epimerizing conditions (methanolic sodium methoxide at reflux for 12 hours), and the reaction products analyzed by gas-liquid phase

chromatography. When the ketone prepared by Jones' method (88) was exposed to the basic conditions and chromatographed, no change in the retention time could be detected upon comparison with the starting material. Bicyclic ketone 41A, prepared by my method (eq. 23) and treated with base, had almost the same retention time as Jones' ketone (88), and differed from the starting material. Co-injection of all four possible stereoisomers showed essentially only two peaks on the gas-liquid phase chromatogram.

The above findings were interpreted as evidence that Jones' ketone (88) was a trans C-5,10 stereoisomer, unable to epimerize, while the other 2-oxa-4-decalone (41A) was an epimerizable cis-ketone, the desired compound.

An explanation of how this epimerization could have occurred under non-basic conditions relies upon the well known mechanism for acid catalyzed enolization (eq. 25). This could have easily occurred during the acid catalyzed acetalization of bicyclic hemiacetal 87 by Jones' method.[74]

Since it seemed that we were dealing with a new 2-oxa-4-decalone, albeit the correct one, for which I could not utilize the existing synthetic sequence, I had to find another way to achieve the desired homologation. However, before attempting this we wanted to confirm the relative stereochemistry of 41A and 88. For example, if our reasoning was correct, we could epimerize 41A to 41B and complete the synthesis as depicted in eq. 24. We also desired to have



(25)

a detailed 270 MHz proton NMR spectral analysis of 41A and 88. From these spectra, we could hopefully assign the chemical shift of the bridgehead protons and determine their coupling constants to provide spectral parameters for the necessary stereochemical evaluation. Finally, we wished to prepare hemiacetal 87 and acetylate it under neutral (101) and epimerizing (102, eq. 26) conditions. After acetylation, we would analyze the compound by GC-mass spectrometry. Should four epimers (101A+B, 102A+B) be found, this would serve as an indication that an anomalous Diels-Alder reaction had not formed 87 with a trans bridgehead; if this were the initial product, no bridgehead epimerization could occur and only

two trans C-1 acetates (102A+B) would be obtained.

To clarify our feeling that the cis-2-oxa-4-decalone (41A) could be converted to its trans epimer (41B), which then would successfully undergo the nitrile homologation procedure (eq. 24), we did the following experiment.[75,76] Epimerization of cis ketone 41A with methoxide gave, at most, a 4:1/trans to cis mixture, as determined by ^{1}H NMR. Formation and fractional crystallization of the mixed methyl-semicarbazones fortuitously led to pure, trans compound (89B) having just one spot by thin layer chromatography. This spot was simlar in R_f to Hsia's methyl semicarbazone (89A), and had a melting point that was just one degree higher. When the two trans methyl semicarbazones were checked for a mixed melting point, a depression of nearly 25 degrees was noted. We felt that these two compounds were C-1-O-methyl acetal epimers. Some evidence for this was that Hsia had determined his acetal to be endo, a C-1 α-O-methyl acetal (2 Hz coupling constant between H-1 and H-10), whereas our compound (41A) must have its C-1-O-methyl acetal in the exo (β) position, exhibiting an ca. 8 Hz H-1 to H-10 coupling constant. The purified, trans methyl-semicarbazone (89B) smoothly formed its HCN adduct at room temperature. Cyano-hydrazine 90B was oxidized with N-bromosuccinimide and the diazene decomposed by sodium methoxide to give the trans nitriles, 91C and D, as in eq. 22.

We had hoped to be able to do a 270 MHz proton spectral analysis of the bridgehead coupling constants for the methyl

semicarbazone derivatives 89A and 95. It was hoped that we could prove that Hsia's compound, 89A, was a trans-fused molecule and that my methyl-semicarbazone (95) was cis. Unfortunately, neither of the two compounds' spectra could be analyzed satsifactorily and we thus relied upon an analysis of 2-oxa-4-decalones 41A and 88 to give us the needed stereochemical information.

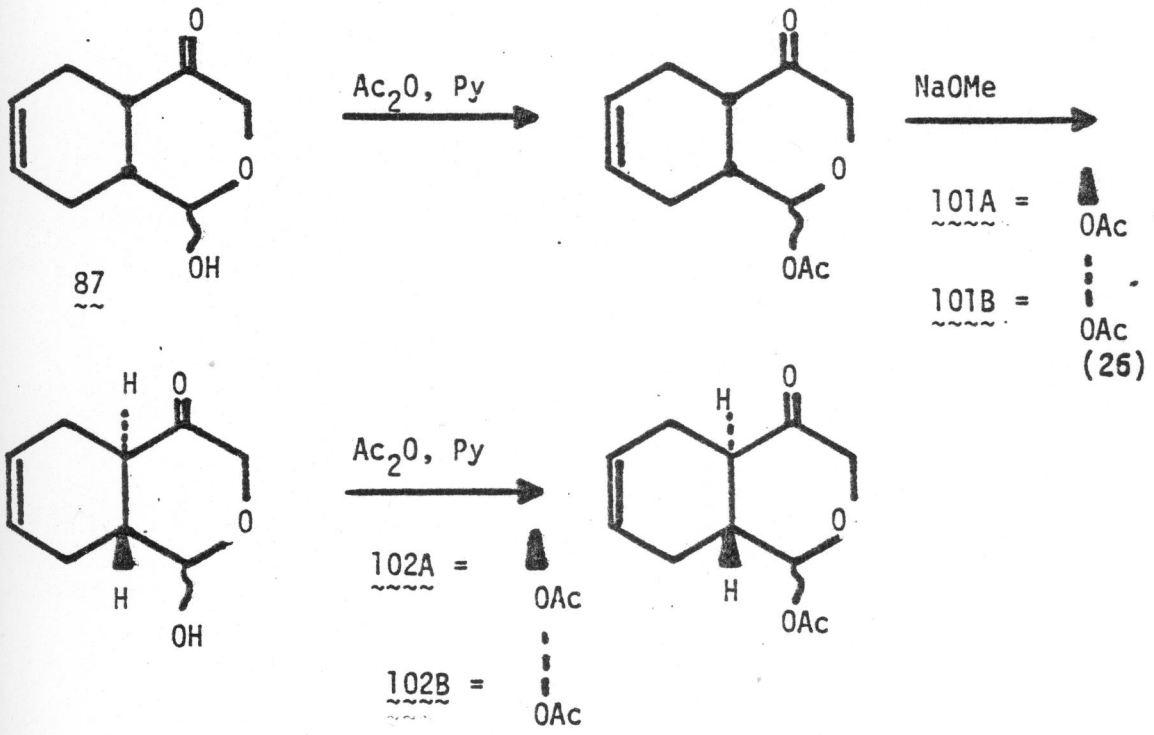
A series of decoupling experiments identified the bridgehead hydrogens: 41A, H-5 at δ_H 3.12 and H-10 at δ_H 2.47; 88, H-5 at δ_H 2.75 and H-10 at δ_H 2.20. Having assigned the desired proton chemical shifts, we used the method of one-half band width analysis to derive the coupling constant of these virtually coupled hydrogens. It was necessary to use this method because these hydrogens were not well resolved, even at 270 MHz.[77,78] In this technique, it is assumed that because there is so much virtual coupling associated with the proton that one is analyzing, the change in $\Delta\nu^{1/2}$ of a given multiplet upon saturation of another hydrogen, which is coupled to the multiplet signal, is proportional to the coupling constant between the observed and decoupled hydrogens. By this method we were able to confirm that the 2-oxa-4-decalone 41A, prepared according to eq. 24, had an H-5 $\Delta\nu^{1/2}$ of about 3.5 to 3.7 Hz when H-10 was irradiated; and an H-10 $\Delta\nu^{1/2}$ of about 3.5 to 3.7 Hz when irradiated at H-5. Jones' 2-oxa-4-decalone (88) had an H-5 $\Delta\nu^{1/2}$ at about 7.9 to 8.1 Hz when irradiated H-10 and an H-10 $\Delta\nu^{1/2}$ of 7.9 to 8.1 Hz when irradiated at H-5. These results indicated, by the

usual Karplus relationship, that the bridgehead at 41A was cis, and that of 88 trans.

Decoupling data located H-1 at δ_H 4.62 for 41A, and for 88, at δ_H 4.67. There was a $\Delta\nu^{1/2}$ of about 2.4 to 3.6 Hz between H-1 and H-10 in 41A, and a $\Delta\nu^{1/2}$ of about 2.4 to 2.8 Hz between H-1 and H-10 in 88. Since a mixed melting point of 89A and 89B showed a depression, and it was felt by reasoning presented before, that 88 has an α, C-1 acetal, it is assumed that the relative stereochemistry in 41A of H-1 and H-10 is trans, the small coupling constant being explained on the basis that a chair, twisted-chair conformation could lead to an H-1, H-10 proton angle of 110 to 130°C.

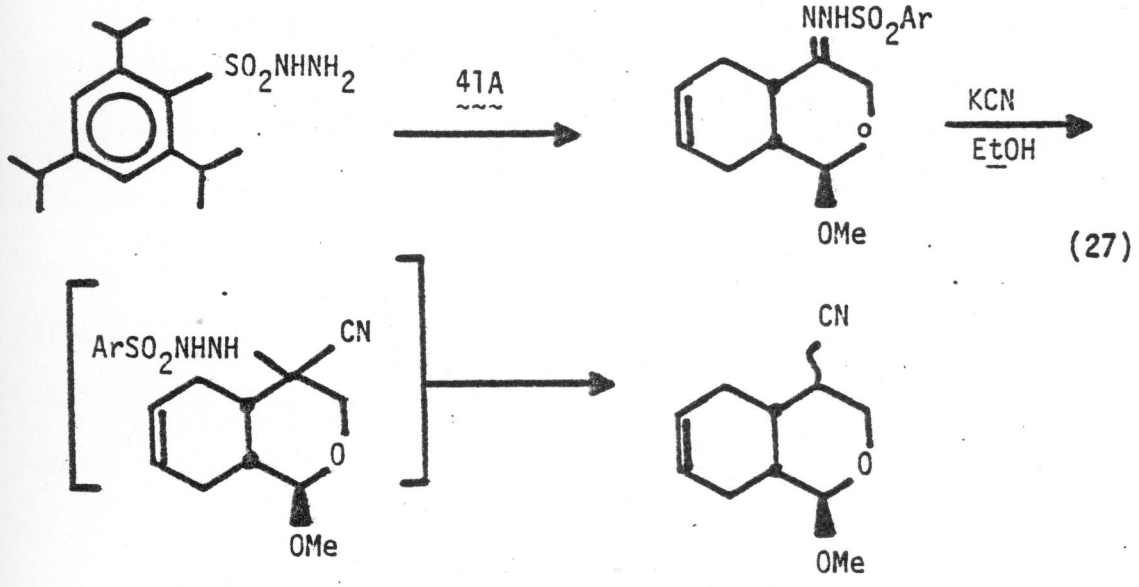
To disprove the possibility that the trans-fusion of 88 had occurred during the Diels-Alder reaction, and not by way of enolization during acetalization, we acetylated hemiacetal 87 before and after exposure to epimerizing conditions (sodium methoxide in methanol). Acetylation of 87 with acetic anhydride in anhydrous pyridine is a mild reaction that would not be expected to epimerize a cis-fused bridgehead if it was present. For this reason the reaction was employed here. The two preparations (101 and 102, eq. 26) were analyzed by GLPC-mass spectrometry and four different acetates found. These results are indirect proof that epimerization of the bridgehead occurred after the Diels-Alder reaction, and not as a result of it. When the cis-bicyclo hemiacetal (87) was acetylated, two products were formed corresponding to C-1 acetate epimers,

101A and B. After treatment of 101 with methoxide, the hemiacetal product was reacetylated and another two stereoisomers formed (102A and B) as a result of the C-5 (bridgehead) epimerization. This gave a total of four stereoisomers, as was found from the mass spectrum of 101 and 102. Had the Diels-Alder reaction given an initial trans product, then only two C-1 acetate epimers would have been found.



With the stereochemistry of Diels-Alder adduct 41A on firm ground, we sought a one-carbon homologation alternative to the

method that had been developed by Hsia. One early attempt at this was to use the triisopropylbenzenesulphonylhydrazide (TPSH) method of Reese. In this procedure, one forms the triisopropylbenzenesulphonylhydrazone of a ketone and then reacts this directly with potassium cyanide in ethanol at elevated temperatures to cause thermolysis of the transient cyano-hydrazine intermediate to a nitrile (eq. 27).[79] This sequence did not work for us when applied



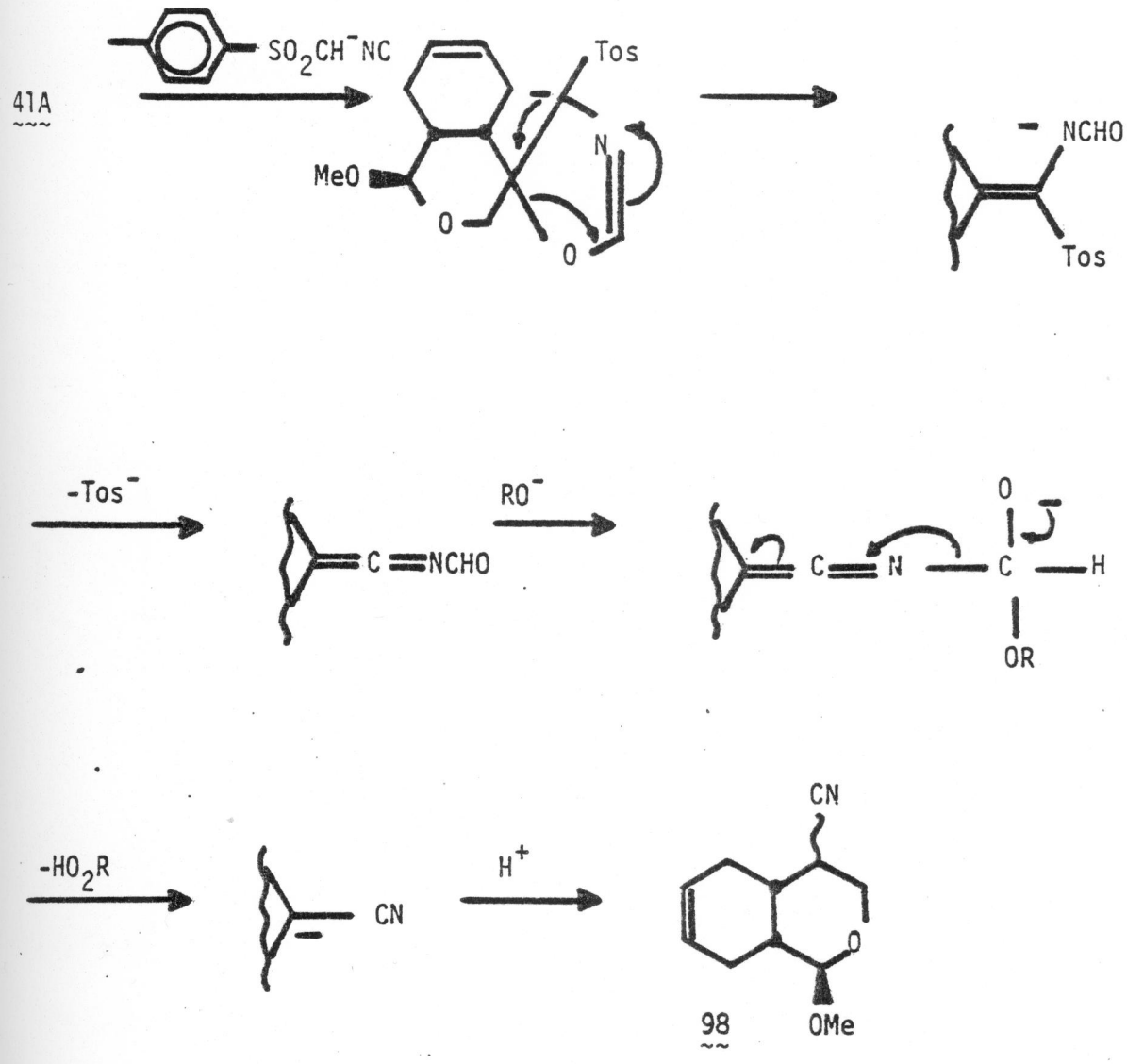
(27)

to 41A. Recent work with TPSH has shown it to be a diimide precursor and this is assumed to have led to side reactions with the isolated double-bond in our molecule.

My co-workers had tried a one-carbon homologation of the trans-2-oxa-4-decalone 88 using tosylmethyl isocyanide (TOSMIC),[80,81] but had had no success with it. Since we were dealing with the cis-fused isomer, we felt that it would be wise to reexamine this homologation reaction. In the TOSMIC reaction (eq. 28), the anion of TOSMIC reacts with ketones to form an intermediate 4-tosyl-1,3-oxazoline intermediate that fragments to give the homolgated nitrile under the influence of the excess base present in the reaction mixture.

After some experimentation with various bases, potassium methoxide was found to be ideal, giving yields of nitriles 98A and 98B as high as 75%. Additionally, it was found that a high degree of kinetic or thermodynamic control could be achieved by varying the temperature of the reaction. For example, the C-4 α nitrile epimer, 98B, was the predominant reaction product at 0°C, but the C-4 β epimer (98A) was the chief product at 20-40°C. Thus we had found a method wherein we could control the stereochemistry of the resulting nitrile.

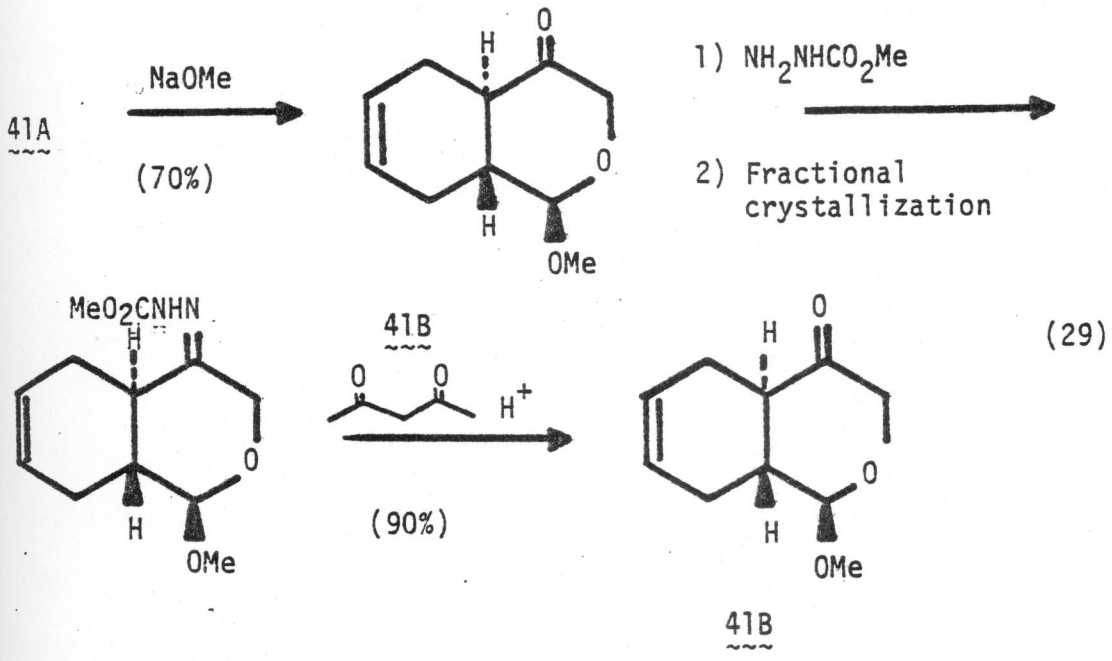
As a means of checking earlier research, we decided to react TOSMIC with the trans bicyclic ketone, 41B. One problem was that in our epimerization experiments we had never gotten more then a 4:1 mixture of trans to cis 2-oxa-4-decalones. Accordingly, we needed a method to separate the trans and cis isomers. This was accomplished quite easily by formation of the mixed methyl semi-



(28)

carbazones of the epimeric mixture and crystallizing out just the trans isomer, 89B. The trans-ketone 41B was then unmasked under

mild conditions by the action of 2,4-pentanedione and an acidic ion exchange resin (eq. 29).[82,83]



(29)

The trans bicyclic ketone 41B did not successfully undergo the TOSMIC reaction and there was some evidence (TLC, NMR) that the trans-ketone may have been isomerized by TOSMIC to yield about 10% of cis nitrile 98.

Because of the strong base ($KOCH_3$-KOtBu) employed in the TOSMIC reaction, and the known predisposition for the cis-2-oxa-4-decalone to epimerize under basic conditions it was imperative to

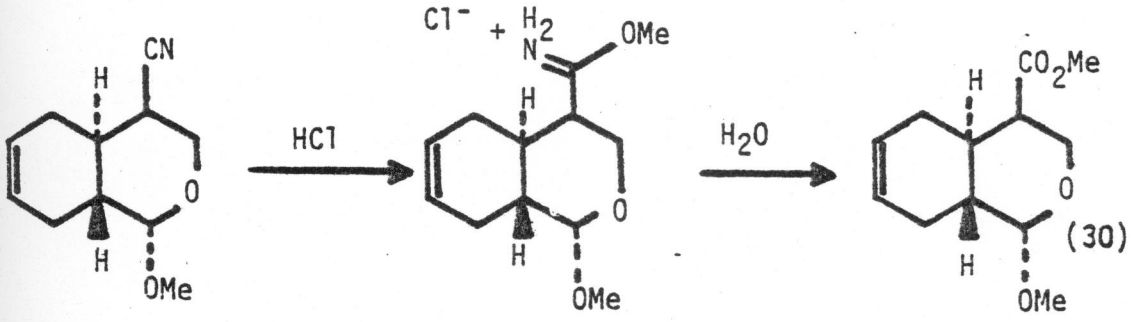
again determine the bridgehead stereochemistry (as well as the relative stereochemistry of the C-4 nitrile epimers) following the cis-2-oxa-4-decalone's conversion to the epimeric nitriles, 98A and 98B.

Our method for determination of the relative stereochemistry of the epimeric nitriles was a 270 MHz ^1H NMR analysis, utilizing the one-half band width method previously discussed. We were able to show, by decoupling experiments, that epimer 98A had H-5 at δ_H 1.77, H-10 at δ_H 1.23, and H-4 at δ_H 2.13; 98B had H-5 at δ_H 2.47, H-10 at δ_H 2.28 and H-4 at δ_H 2.82. When irradiated at H-10, 98A had an H-5 $\Delta\nu^{1/2}$ of 3.6 to 4.0 Hz, and an H-5 $\Delta\nu^{1/2}$ of 3.4 to 3.6 Hz when irradiate at H-4. Epimer 98B had an H-5 $\Delta\nu^{1/2}$ of 3.4 to 3.6 Hz when irradiated at H-10, and an H-5 $\Delta\nu^{1/2}$ of 8.9 to 9.1 Hz when irradiated at H-4. These coupling constants enabled us to describe the bridgehead stereochemistry as cis for both epimers, with the C-4 nitrile β in 98A and α in 98B.

All that remained at this point, for completion of the synthetic goal, was hydrolysis of the nitrile to form the methyl ester, 7A. This was not accomplished as easily as it appeared that it would be at first.

Originally, Hsia had tried two different methods to prepare the desired ester from the nitrile. The first hydrolysis method Hsia used was a direct conversion of the nitrile to its corresponding methyl ester by way of the imidate salt, 103.[84] In this approach (eq. 30), an imidate salt is formed from the nitrile by the action of

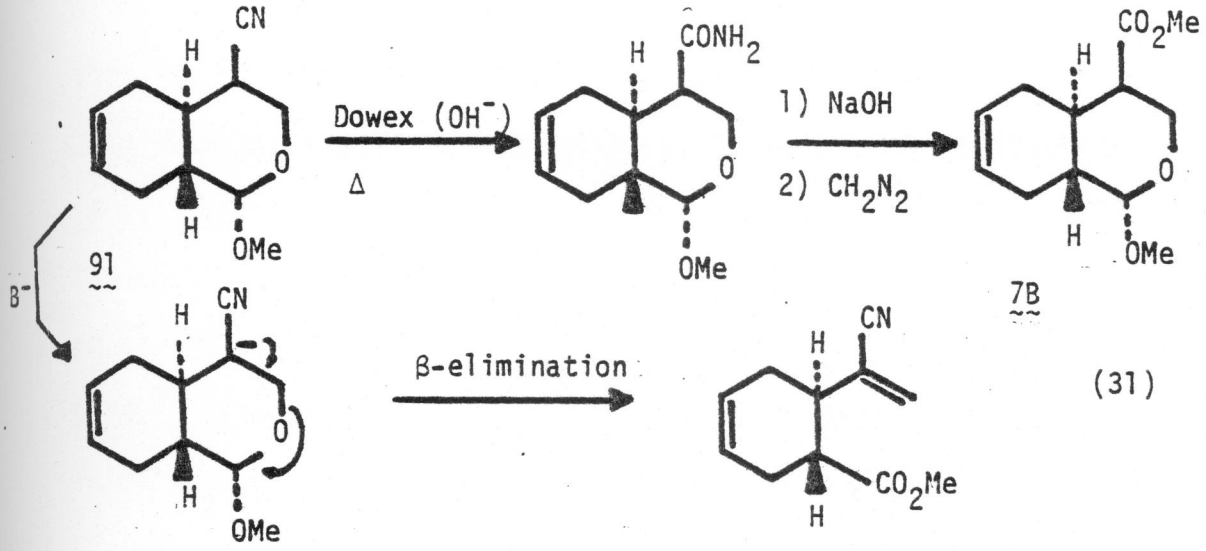
dry hydrogen chloride in an anhydrous methanol-ether solution. This intermediate is then decomposed to the desired ester by water during the work-up. Due to the acid sensitive nature of the C-1-O-methyl acetal, there seems to be little precedent for the success of this method. Indeed, the reaction did not give Hsia the desired transformation, but seems to have led to molecular decomposition.



(30)

91 103 7B

The second method was a two step hydrolysis of 91 to its acid, by way of the amide (eq. 31), followed by esterification with diazomethane, giving Hsia the methyl ester (7B) in 47% overall yield, from nitrile 91.[85] Hsia had found the two step hydrolysis necessary because there was a tendency for the molecule to decompose if strong base was used to directly hydrolyze the nitrile to the acid. This may have been due to formation of olefin 104 by way of β-elimination, because UV-absorbing products were observed in the crude reaction mixture by TLC analysis (eq. 31).

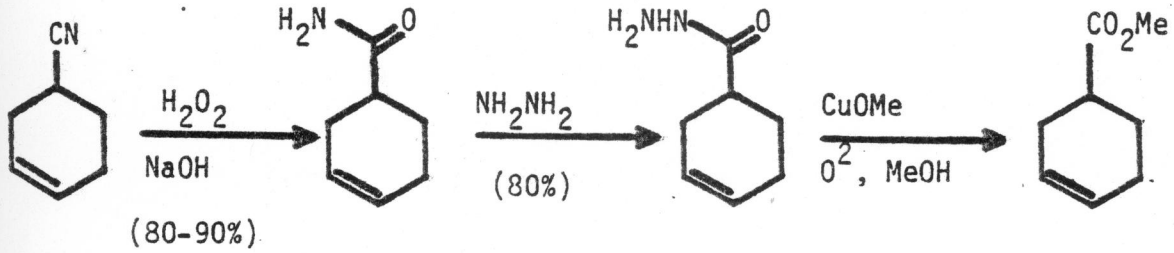


When the nitrile 98 prepared from the cis-2-oxa-4-decalone 41A was treated with Hsia's two step hydrolysis procedure, the first hydrolysis step did give an amide in acceptable yield, but this amide failed to form the carboxylic acid under the strongly basic condtions of the second step. In fact, only UV-absorbing TLC spots were formed, leading us to believe that β-elimination had predominated.

At this point, it became necessary to develop a means by which nitriles could be converted to their corresponding methyl esters

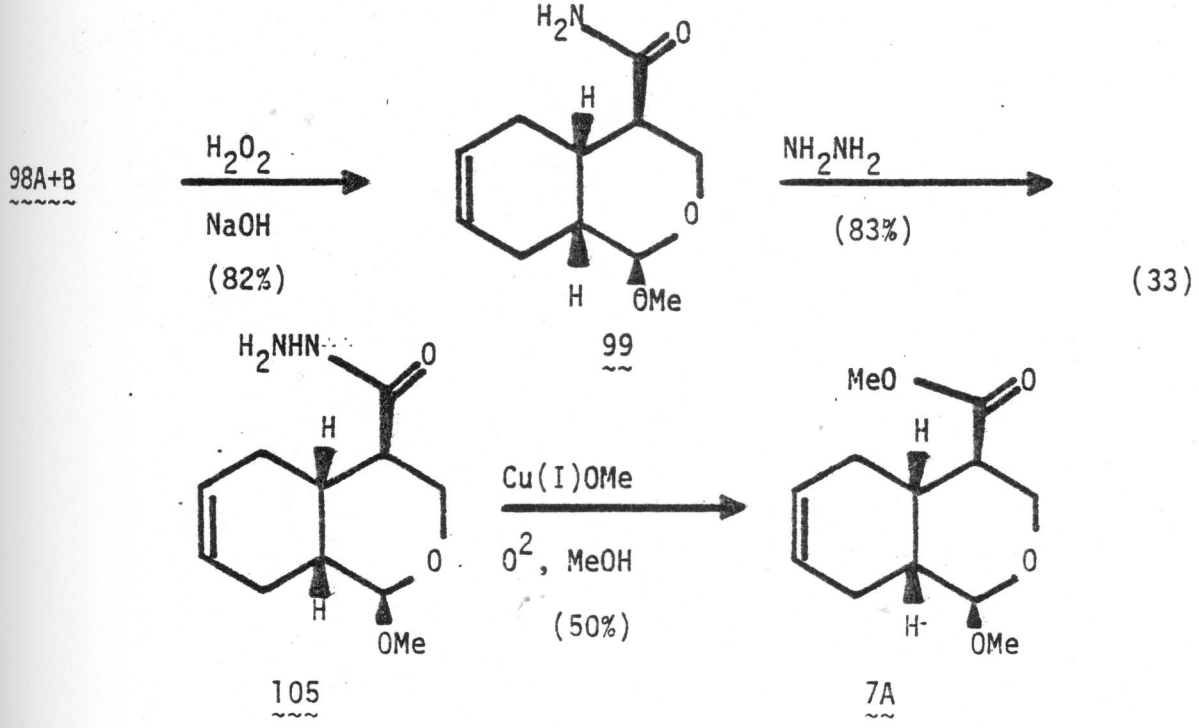
using mild conditions. This is a classical problem because the cyanide anion is often used to effect a one-carbon homologation, to be subsequently converted to an acyl function. With the exception of one report[86] (which I tried and found not to work), it seems that this has not previously been accomplished under mild conditions.

Our strategy in the hydrolysis of the nitrile is illustrated in eq. 32 for the model compound, 3-cyclohexene-1-carbonitrile. The model nitrile was converted to a primary amide by the action of weakly alkaline hydrogen peroxide in ethanol at reflux temperature.[87] The yields were good (ca. 80%) but somewhat variable. This amide was converted to an acyl hydrazide in 80% yield by the action of refluxing hydrazine hydrate in ethanol.[88] The resulting acyl hydrazide was converted to its methyl ester by the method of Tsuji, which involves the oxidation of an acyl hydrazide with air in the presence of copper (I) methoxide.[89] The yield of this material could not be accurately recorded due to its high volatility.



(32)

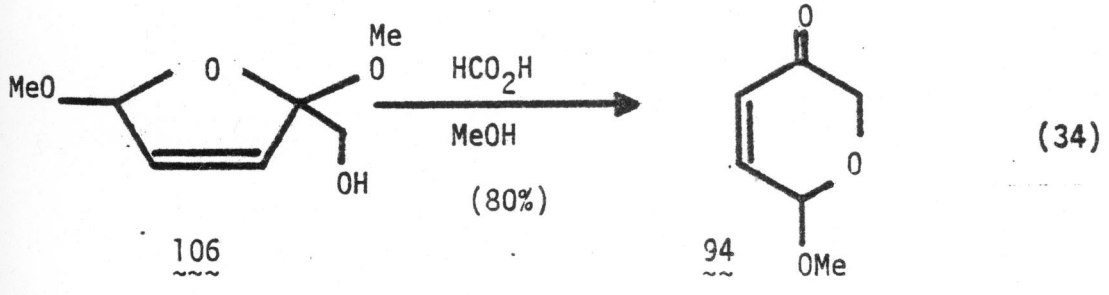
Having accomplished the model transformation we proceeded to carry out this reaction sequence with the cis nitriles, 98A and 98B. Since we had control over the nitrile's C-4 stereochemistry, we hoped that our subsequent hydrolyses would not epimerize that center. Unfortunately, this was not to be the case as we found that epimerization, presumably to the thermodynamically preferred β isomer, occurred during the hydrolysis of the α and β nitriles to form just one amide. The route used is shown in eq. 33, and was much the same as for the model compound, with the notable exception that the acyl hydrazide's (105) formation was much slower than for the model compound, taking four days at 150° in a sealed tube. The yield of the



(33)

cis-methyl ester, 7A, was 50% from 105. A second method was also tried to hydrolyze the acyl hydrazide to the ester. Although we were not successful using Kametant's method (refluxing the hydrazide in an alcoholic solution containing one equivalent of chloral), I feel that the reaction does have potential uses for a circumstance like this.[90,91]

In closing this section, I would like to highlight one of our most useful discoveries. Our original method for acetalizing the C-1 hemiacetal, 86, involved refluxing 86 for 36 hours in a solution of methanol and trimethyl orthoformate with a magnesium sulfate catalyst-drying agent. The yield of the impure acetal (94) ranged from 40 to 65%.[72] This not very facile acetalization was later supplanted by a method developed at Pfizer Pharmaceuticals. In this reaction, the 2,5-dimethoxy-dihydro-furanol (106) was rapidly converted to 94 in the presence of 98% formic acid in anhydrous methanol, giving a very pure product in 80% yield (eq. 34).[92]



106 94 (34)

Because the enone (94), prepared as above, was so pure, we were able to assay its crucial Diels-Alder reaction with butadiene more carefully than previously done by Hsia and Mattes.[93] By experimenting with different types and quantities of Lewis acids, we were able to develop the reaction conditions so that it gave us an 85% yield of 41A at -50°C, atmospheric pressure, and in one to two hours. This is compared to the earlier work which gave a 30-40% yield of 41A at 1,000 PSI, three days, and 110°C.

IV. Experimental

Melting points were determined on a Fisher-Johns hot stage melting point apparatus. Mass spectra were obtained on a Finnigan model 1015 spectrometer with a model 6000 data processing unit. Mass spectra of selected samples were run on a Dupont 21-491B mass spectrometer interfaced to a Varian 2740 GC and Nova 2 data system. Nuclear magnetic resonance spectra were taken on Varian EM-390, Bruker 90, or 270 MHz NMR spectrometers. Chemical shifts are reported in ppm from TMS. IR data were obtained from Perkin-Elmer models 257 and 557 recording spectrophotometers. UV spectra were obtained from a Cary model 14 recording spectrophotometer. Column chromatography utilized MN silica gel, 70-270 mesh. TLC was performed on Brinkman precoated silica gel F-254 plates, spots being visualized under UV light or by potassium permanganate spray (2% in water). Organic extracts were dried over anhydrous $MgSO_4$. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Rotary evaporation was done on a Büchi rotary evaporator at reduced pressure, using either a water aspirator or an oil pump.

2,5-Dimethoxy-2,5-dihydrofurfuryl alcohol (106). Freshly distilled furfuryl alcohol was added to a solution of absolute MeOH (0.8 mL MeOH: mmol furfuryl alcohol) and NH_4Br (0.1 equiv). This solution was poured into an electrolysis cell (brass anode and carbon cathode), externally cooled to -25°C (with a dry ice-ethanol water bath). The magnetically stirred solution was electrolyzed for 18 h

at 1.5 amps (ca. 1 Faraday). Solid NaOMe (0.1 mol equiv) was added to neutralize the HBr formed in the reaction. The MeOH was removed by rotary evaporation and the residue redissolved in benzene (0.6 mL: mmol furfuryl alcohol). The solution was suction filtered through a pad of neutral alumina (0.08 g Al_2O_3: mmol furfuryl alcohol, Woelm, activity grade I). The alumina was washed with an equal volume of benzene and the combined filtrates were evaporated free of solvent. The crude 106 was distilled through a 4.0 cm Vigeraux column to give 106 in 65-78% yield:[94] bp 65-70°C at 0.20-0.25 Torr, Lit.[94] bp 71°C at 1.0 Torr; TLC (EtOAc-Et_2O, 15:1) R_f = 0.40; ^{1}H NMR ($CDCl_3$) δ 3.22 (s, 3H, OCH_3) 3.50 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.63 (m, 2H, CCH_2O), 5.50 (s, 1H, acetal proton), 6.05 (q, 2H, J = 5 Hz, vinyl protons).†

4,5-Dehydro-pyran-3-one-6-ol (86). The 2,5-dimethoxy-2,5-dihydrofurfuryl alcohol 106 was dissolved in 2% aqueous H_2SO_4 (2 mL/gram) and the solution magnetically stirred for 10 min at 22°C. The solution was titrated to pH 4 by the addition of solid $NaHCO_3$ and the volume reduced by exactly one-half on the rotary evaporator. This solution was extracted with CH_2Cl_2 (5 x 4 mL/gram), the combined organic extracts were dried, filtered and the solvent removed in vacuo to yield crude 86 in 75-90% yield. The crude product crystallizes on storage at 4°C to form a translucent solid, mp 54-58°C.

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†The NMR spectrum of this material is not included in the appendix.

My experience has shown that 86 has toxic properties and should not be directly handled. Also, the vapor is harmful to the eyes. TLC (EtOAc-Et_2O, 15:1) R_f = 0.30; ^1H NMR ($CDCl_3$) δ 3.85 (br, 1H, OH), 4.32 (ABq, 2H, J = 18 Hz, CCH_2O), 6.16 (d, 1H, J = 11 Hz, vinyl proton), 6.98 (d of d, 1H, J = 11 and 3 Hz, vinyl proton).

4,5-Dehydro-pyran-3-one-6-methoxy (94). Method A. In oven dried glassware the hemiacetal 86 (5.7 g, 0.05 mol) was mixed with freshly distilled trimethyl orthoformate (75 mL, 0.64 mol), anhydrous MeOH (1.5 mL, 0.047 mol) and anhydrous $MgSO_4$ (15 g, 0.17 mol). The solution was refluxed, with a drying tube and magnetic stirring rod, for 36 h. After the reaction cooled, the mixture was decanted and as much of the reaction solvent poured off as possible without disturbing the $MgSO_4$. The reaction mixture remaining in the flask was extracted with EtOAc (6 x 80 mL) by decanting the mixture each time except the last, when the $MgSO_4$ was not allowed to settle but poured into the filter and the adhering solvent removed by suction filtration. The filtrates were combined, refiltered and the solvent removed in vacuo to give 94 as a colorless gum in ca. 40-66% yield. The gum can be recrystallized from Et_2O-hexane, (8:1) at less than 0°C, to give long spar-crystals, pale brown in color, mp 20-24°C. The C-4 ketal impurities are clearly seen in the ^1H NMR spectrum of crystalline 94.[72] TLC (EtOAc-hexane, 1:3) R_f = 0.60; ^1H NMR ($CDCl_3$) δ 3.50 (s, 3H, OCH_3), 4.25

(ABq, 2H, J= 18 Hz, CCH_2O), 5.10 (d, 1H, J = 3 Hz, acetal proton), 6.15 (d, 1H, J = 10.5 Hz, vinyl proton), 6.92 (d of d, 1H, J = 10.5 and 3 Hz, vinyl proton); MS, m/e (rel intens) 128 (25), M^+, 96 (100), 84 (35), 68 (55).

Method B. The dimethoxy furanol 106 (19.2 g, 0.12 mol) was mixed with 8 mL of anhydrous MeOH (0.25 mol), and the solution poured into a dropping funnel. HCO_2H (97%, 80 mL, 1.7 mol) was combined with 4 mL of freshly distilled MeOH in a single necked, 250-mL round bottom flask. The system was protected from moisture with a drying tube on top of the addition funnel. The solution of 106 was added over a 15 minute period to the rapidly stirred MeOH-HCO_2H solution at room temperature. After the addition was complete, the reaction was allowed to stir for five more minutes, then it was poured into 200 mL of H_2O and extracted with $CHCl_3$ (3 x 100 mL). The combined organic extracts were washed with $NaHCO_3$ solution (100 mL), then brine (100 mL) and dried. After filtration and removal of the solvent in vacuo, the crude 94 was obtained as a colorless liquid (12.3 g, 0.096 mol, 80%). The crude product was found to be pure enough for subsequent work, especially with regard to its low content of the C-4 ketal.

Cis-7,8-dehydro-1-methoxy-2-oxa-4-decalone (41A). The dienophile, 94 (7.523 g, 0.0587 mol), was dissolved in CH_2Cl_2 (75 mL) and poured into a jacketed dropping funnel, the jacket of which was cooled to -70° to -80°C with dry ice and ethanol. The dropping

funnel was connected to an oven dried, three necked, 500-mL round bottom flask into which butadiene (97 mL, 1.79 mol, 35 equiv) had been condensed and mixed with CH_2Cl_2 (redistilled, 175 mL) and $AlCl_3$ (3.0 g, 22.5 mmol, 0.38 equiv). The flask and dropping funnel were purged with dry nitrogen, and the reaction mixture was stirred magnetically. The round bottom flask was cooled to -78°C in an ethanol-dry ice bath. After sufficient time to allow for thorough cooling, the solution in the dropping funnel was run into the solution of butadiene and $AlCl_3$. This took about 10 min, care being exercised that good stirring and cooling were maintained during the addition. After completing the addition at 94, the reaction mixture was stirred for an additional 10 min before warming to -50°C by replacing the dry ice-ethanol bath with one containing chloroform-dry ice. The reaction mixture was stirred for about 1.0 h more at this temperature. The reaction's progress was followed by TLC using EtOAc-hexane, 1:3, as a solvent system. Aliquots were quenched immediately with aqueous $NaHCO_3$ before TLC analysis; otherwise, the aliquots continued to react rapidly at room temperature and indicated premature progress of the reaction.

After completion, the cold reaction mixture was poured into a magnetically stirred, 2-liter beaker containing crushed ice and $NaHCO_3$ solution (1 liter total). The quenched reaction mixture was allowed to warm up to room temperature, then it was suction filtered through a 15 cm Büchner funnel containing 9.0 g of Celite.

The aqueous filtrate was extracted with CH_2Cl_2 (3 x 175 mL), and the combined organics were washed once with $NaHCO_3$ solution, (100 mL) and once with brine (100 mL). The organic solution was dried for 30 min, filtered, and the solvent removed in vacuo. The crude product was fractionally distilled through a 2.5 cm Vigeraux column attached to a short path distillation apparatus to give 41A as a fraction distilling between 130-134°C at 10-12 mMHg, 9.11 g, 50.0 mmol, 84%, as a pale yellow liquid;[93] TLC (EtOAc-hexane, 1:3) R_f = 0.70; IR ($CHCl_3$) ν 2900, 1720 (C=O), 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ ca. 2.15 (m, 3H), 2.30-2.90 (m, 2H), ca. 3.11 (m, 1H), 3.47 (s, 3H, OCH_3), 4.00 (ABq, 2H, J = 16.5 Hz, CCH_2O), 4.58 (d, 1H, J = 3 Hz, acetal proton), 5.57 (s, 2H, vinyl protons).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92, H, 7.73. Found: C, 66.00; H, 7.91.

Methyl semicarbazone of cis-7,8-dehydro-1-methoxy-2-oxa-4-decalone (95). The cis-2-oxa-4-decalone 41A (346 mg, 2.0 mmol) was mixed with methyl carbazate (0.18 g, 2.0 mmol, recrystallized from benzene-cyclohexane, 3:1, mp 70-73°C), absolute EtOH (3.8 mL, commercial) and 3.8 uL of glacial HOAc. The reaction mixture was refluxed for 15 min with magnetic stirring, then was allowed to cool at 0°C overnight to cause crystallization of the methyl-semicarbazone, 95. Filtration of the small, colorless spar-crystals in a Craig tube gave 472 mg, 93% of 95;[78] mp, variable, 166-168°C; TLC (EtOAc-hexane, 1:3) R_f = 0.67 and 0.72 (syn and anti isomers);

IR (KBr) ν 3470 (NH), 3160, 3020, 1740 (C=O), 1722 (C=O), 1545, 1535 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (m, 5H), 2.90 (m, 1H), 3.40 (s, 3H, OCH_3), 3.80 (s, 3H, CO_2CH_3), 4.31 (ABq, 2 H, J = 11.3 Hz, CCH_2O), 4.57 (d, 1H, J = 8 Hz, acetal proton), 5.71 (br, 2H, vinyl protons), ca. 8.31 (br, 1H, NH); UV (MeOH) 215 (ε = 17,462); MS, m/e (rel intens) 254 (3) M^+, 222 (50), 193 (32), 79 (100).

Anal. Calcd for $C_{12}H_{18}O_4N_2$: C, 56.68; H, 7.13; N, 11.0. Found: C, 56.83; H, 7.27; N, 11.07.

Cyano-hydrazine derivative of cis-7,8-dehydro-1-methoxy-2-oxa-4-decalone (96). The methyl semicarbazone derivative 95 (659 mg, 2.6 mmol) was added to a 50 mL round bottom flask equipped with a reflux condenser, containing anhydrous MeOH (16 mL) and anhydrous KCN (1.0 g, 15 mmol, 6 equiv). Glacial HOAc (3.25 mL) was then added to the reaction mixture and the solution refluxed for a total of 18 h, with magnetic stirring and under a N_2 atmosphere. At this time, TLC (EtOAc-hexane, 1:1) showed that most of the UV-active starting material had been consumed, and the solvent was removed in vacuo. The residue was dissolved in 15 mL of H_2O and extracted with $CHCl_3$ (3 x 20 mL). The combined organics were washed with $NaHCO_3$ solution (50 mL), then brine (50 mL), and dried for 30 min. The $CHCl_3$ solution was filtered and the solvent removed in vacuo to give a white semi-solid. This material was dissolved in two mL of EtOAc and chromatographed through a 1.5 x 20 cm silica gel column, using an Et_2O-EtOAc, 2:1, solvent system. Aliquots of

10 mL were collected and 96 was found in aliquots three and four. After removal of the solvent, a clear, glassy oil, 96, remained, 606 mg, 83%;[75] TLC (EtOAc-hexane; 1:3) R_f = 0.80; IR (KBr) ν 3280 (NH), 2900, 1715 (C=O), 1453, 1350, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ ca. 2.12 (m, 2H), ca. 2.48 (m, 3H), ca. 2.68 (m, 1H), 3.43 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.88 (ABd, 2H, J = 5 Hz, CCH_2O), 4.46 (d, 1H, J = 2.6 Hz, acetal proton), 4.68 (d, 1H, J = 5 Hz, CHNHNH), 5.74 (s, 2H, vinyl protons), 6.33 (d, 1H, J = 5 Hz, $NHNHCO_2CH_3$); MS, m/e (rel intens) 254 (4), 250 (36), 79 (100).

Base catalyzed epimerization of cis-7,8-dehydro-1-methoxy-2-oxa-4-decalone (41A). The cis-decalone, 41A (1.588 g, 8.56 mmol), was added to a 0.174 molar solution of NaOMe/methyl alcohol-d_1 (from 23 mg of fresh sodium in 5.0 mL of methyl alcohol-d_1) in a 15-mL round bottom flask equipped with a stirring bar, reflux condenser, and purged with a N_2 atmosphere. The solution was stirred at reflux for 12 h. After cooling, the reaction mixture was filtered through 4.0 g of dry acidic ion exchange resin to neutralize the NaOMe. The resin was washed once with 20 mL of MeOH and the combined filtrates evaporated in vacuo to give the mixture of deuterated decalones (1.32 g, 85%). ^1H NMR showed that about 60% epimerization had occurred. The mass spectrum showed a mass increase of three, indicating that all of the exchangeable sites were occupied by deuterium. This was confirmed by the loss of the AB quartet (2 H, at 4.00 ppm, normally) and the multiplet (1 H) normally at ca. 3.11

ppm, in its proton NMR spectrum. TLC (EtOAc-hexane, 1:3) R_f = 0.63 (41B) and 0.56 (41A); MS, m/e (rel intens) 185, M^++3 (10), 184, M^++2 (7), 183, M^++1 (5), 182, M^+ (1), 154 (7), 153 (17), 152 (6), 80 (100).

GLPC analysis of cis and trans-7,8-dehydro-1-methoxy-2-oxa-4-decalones (41A + B) and (88). To analyze the epimeric mixture of 41A+B and 88, a Chicago-Nuclear GC was used with a 3%-OV 17, 100/120 Gas-Chrom Q column (6 foot x 3/16 inch ID). The column temperature was 140°C, injector temperature was 290°C, and the FID detector temperature was 400°C. The rate of N_2 carrier gas flow was 47 cc per minute. The samples were dissolved in CH_2Cl_2 (1-2 uL: mL CH_2Cl_2) and 1.0-3.5 uL injections were made. The chart speed was 4.0 inches per minute. 88 and 41A represent the standard 2-oxa-4-decalones. 88Σ and 41B represent the 2-oxa-4-decalones which were exposed to epimerizing conditions (NaOMe-MeOH).

Trial	Sample	Retention Time (minutes)	Peak height
1	88	7.89	100%
2	88Σ	7.89	100%
3	41A	8.02	100%
4	41B	7.89/8.02	ca. 90/10%
5	41A + 88	7.89/8.02	40/60%
6	88 + 88Σ	7.89	100%
7	41 + 41B	7.89/8.02	65/35%
8	88 41B	7.89/8.02	90/10%

Methyl semicarbazone of trans-7,8-dehydro-1-methoxy-2-oxa-4-decalone (89B). The epimeric mixture of cis and trans [3,3,5-^{2}H] 2-oxa-4-decalones (1.32 g, 0.73 mmol, 41A+B) was mixed with methyl carbazate (0.65 g, 7.3 mmol, 1 equiv), absolute EtOH (8 mL, commercial) and glacial HOAc (3 uL), and treated as given above for 95. The initially formed crystals of the methyl semicarbazone were dissolved in 1.2 mL of boiling anhydrous MeOH and allowed to crystallize once more to give 0.96 g, 52%, of the pale, spar-crystals: mp 169°-171°C;[75] mixed mp with 89A, 139-158°C; TLC (EtOAc-hexane, 1:3) R_f = 0.72; IR (KBr) ν 3485 (NH), 3240 (NH), 3135, 2905, 2835, 1708 (C=O), 1693 (C=O), 1475, 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ ca. 1.55-2.75 (m, 6H), 3.40 (s, 3H, OCH_3), 3.82 (s, 3H, CO_2CH_3), ca. 4.15-4.61 (m, 3H, CCH_2O and acetal proton), 5.70 (s, 2H, vinyl protons), 7.93 (s, 1H, NH); UV (MeOH) 215 (ε = 17,462); MS, m/e (rel intens) 257, M^++3 (38), 225 (100), 196 (23).

Anal. Calcd for $C_{12}H_{18}O_4N_2$: C, 56.68; H, 7.13; N, 11.00. Found: C, 56.81; H, 7.27; N, 10.94.

Cyano-hydrazine derivative of trans-7,8-dehydro-1-methoxy-2-oxa-4-decalone (90B). The trans methyl semicarbazone derivative 89B (0.30 g, 1.2 mmol) was added to a 25-mL round bottom flask equipped with a reflux condenser, stirring bar, and containing anhydrous MeOH (16 mL) and dry KCN (0.468 g, 7.2 mmol). Glacial HOAc (0.55 mL) was then added to the reaction mixture and the solution refluxed for 18 h under a N_2 atmosphere. At this time, TLC

(EtOAc-hexane, 1:1) showed that most of the UV-active starting material had been consumed. Then, the solvent was removed by rotary evaporation in vacuo. The resulting residue was dissolved in H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined solvent was removed in vacuo to yield 90B (0.3455 g, 91% crude yield). This material was column chromatographed on a 15 x 1.5 cm silica gel column using EtOAc-hexane, 3:2, as a solvent system. The fractions containing the two C-4 epimers of 90B were combined and evaporated to give a light brown glass (297 mg, 88%). This material was recrystallized from EtOAc-hexane (1:5) to give one C-4 epimer of 90B (R_f = 0.40) [The other C-4 epimer of 90B was present in 9:1 excess in the mother liquor (R_f = 0.30)]: mp 190°-192°C;[75] TLC (EtOAc-hexane, 1:1) Rf = 0.40 and 0.30 (C-4 epimers); IR ($CHCl_3$) ν 3405 (NH), 3300 (NH), 2230 (CN), 1725 (C=O), 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.82 (m, 3H), 2.30 (m, 3H), 3.46 (s, 1H), 3.50 (s, 3H, OCH_3), 3.77 (s, 3H, CO_2CH_3), 4.08 (m, 1H, acetal proton), 4.27 (m, 2H, CCH_2O), 5.66 (d, 2H, J = 3 Hz, vinyl protons), 6.31 (m, 1H, $NHCO_2CH_3$); MS, m/e (rel intens) 281, M^+ (28), 250 (90), 219 (100).

Anal. Calcd for $C_{13}H_{19}O_4N_3$: C, 55.50; H, 6.75; N, 14.93. Found: C, 55.83; H, 7.03; N, 14.60.

trans-7,8-Dehydro-1-methoxy-2-oxadecalin-4-carbonitrile (91C+D). Redistilled CH_2Cl_2 (10.3 mL), anhydrous pyridine (48 mg, 1 equiv), and the cyano-hydrazine derivative 90B (171 mg, 0.607 mmol) were mixed in an oven dried, 25 mL round bottom flask equipped

with a stirring bar and purged with N_2. After thoroughly cooling the solution in a water-ice bath, N-bromosuccinimide (108 mg, 1 equiv, mp 180-183°) was added, whereupon the solution turned a bright yellow color. The reaction was stirred for an additional h at 0-5°C. At that time TLC (EtOAc-hexane, 1:1) indicated that the reaction was complete (only two UV-active spots on the chromatogram). The reaction mixture was washed with 10% aqueous K_2CO_3 solution (2 x 10 mL), then H_2O (1 x 10 mL) and dried. The solution was filtered and the solvent removed *in vacuo*. The crude yellow diazene (163 mg) was evacuated for 1.0 h on a high vacuum line to remove the last traces of pyridene.[75]

The crude diazene was dissolved in 0.6 mL of anhydrous MeOH and added, dropwise, from a syringe, over a period of ten minutes, to a cooled (0-5°C) 0.83 M solution (0.4 mL) of NaOMe in MeOH in a 5.0 mL round bottom flask equipped with a stirring bar and protected by a N_2 atmosphere. Immediate loss of the intense yellow color, as well as vigorous evolution of N_2 gas occurred. TLC showed the complete loss of UV-absorbing material. After 15 minutes the reaction was neutralized by the addition of glacial HOAc (17.4 mg, 1 equiv). The solvent was removed *in vacuo*, the resulting residue dissolved in CH_2Cl_2 (3 mL), filtered, and organic solution was dried, filtered, and most of the solvent removed by rotary evaporation. The concentrated liquid was purified by PLC in EtOAc-hexane, 1:2. The two non-UV absorbing bands were each eluted with 25 mL of CH_2Cl_2

and the solvent removed *in vacuo* to give **91C** (R_f = 0.83; 25 mg) and **91D** (R_f 0.63; 65 mg) as colorless glasses for a 77% overall yield.[75]

91C: IR ($CHCl_3$) ν 2850, 2240 (CN), 1725 (imp), 1600 (C=C), 1512 cm^{-1}; ^1H NMR ($CDCl_3$) δ *ca.* 1.5-3.8 (m, 6H), 3.53 (s, 3H, OCH_3), 3.76 (d, 1H, *J* = 12 Hz), 4.08 (d, 2H, *J* = 8 Hz), 4.30 (d of d, *J* = 12 and 4 Hz), 5.71 (m, 2H, vinyl protons); MS, *m/e* (rel intens) 193, M^+ (19), 161 (18), 79 (100).

91D: IR ($CHCl_3$) ν 2850, 2240 (CN), 1512 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (m, 3H), *ca.* 2.15 (m, 2H), 2.70 (s, 1H), 3.44 (s, 3H, OCH_3), 3.94 (m, 2H), 4.23 (d of d, 1H, *J* = 12 and 2 Hz), 5.61 (d, 2H, *J* = 2 Hz, vinyl protons); MS, *m/e* (rel intens) 193, M^+ (9), 161 (4), 79 (100).

270 MHz ^1H NMR analysis of *trans*-7,8-dehydro-1-methoxy-2-oxa-4-decalone (88). From structural inspection, H-10 should have appeared as a 12 line pattern, but the signal appeared as an octet at 2.20 ppm due to coalescence. For H-5, I expected a six line pattern, from a doublet of triplets. This was observed at 2.75 ppm.

Decoupling data located the H-1, H-5 and H-10 resonances, and enabled me to determine the approximate coupling constants of these signals. Analysis of the coupling constants was done by measuring the width of a given multiplet at its one-half height ("one-half band width") and subtracting this figure from the one-half band width ($\Delta\nu^{1/2}$) of the decoupled signal. The difference is the approximate coupling constant.[78]

Proton observed	J ($\Delta\nu^{1/2}$)	ΔJ ($\Delta\nu^{1/2}$)	Proton irradiated
H-1, 4.67 ppm	ca. 5.9-6.1 Hz	no change	H-5
H-1	5.9-6.1	ca. 2.3-2.5 Hz	H-10
H-5, 2.75 ppm	31.9-32.1	no change	H-1
H-5	31.9-32.1	7.9-8.1	H-10
H-10, 2.20 ppm	37.1-37.3	2.4-2.8	H-1
H-10	37.1-37.3	7.9-8.1	H-5

By aliphatic Karplus equation and Drieding models: Θ H-5, H-10 = ca. 165° = 7.9-8.1 Hz (trans).

Θ H-1, H-10 = ca. 65° = 2.4-2.8 Hz (cis).

270 MHz ^{1}H NMR analysis of cis-7,8-dehydro-1-methoxy-2-oxa-4-decalone (41A). From structural inspection, H-10 should appear as a 12 line pattern, a doublet of triplets of doublets, which was found at 2.47 ppm. H-5 was expected to be a six line pattern, from a doublet of triplets, but the signal was a multiplet at 3.12 ppm.

The spectral parameters were measured in the same way as given for the preceding experiment.

Proton observed	J ($\Delta\nu^{1/2}$)	ΔJ ($\Delta\nu^{1/2}$)	Proton irradiated
H-1, 4.63 ppm	ca. 4.7-4.9 Hz	no change	H-5
H-1	4.7-4.9	ca. 2.3-2.5 Hz	H-10
H-5, 3.12 ppm	23.9-24.1	no change	H-1
H-5	23.9-24.1	3.5-3.7	H-10
H-10, 2.47 ppm	19.1-19.3	2.3-2.5	H-1
H-10	19.1-19.3	3.5-3.7	H-5

By aliphatic Karplus equation and Drieding models: θ H-5, H-10 = ca. 65° = 3.5-3.7 Hz (cis).

θ H-1, H-10 = ca. 115° = 2.3-2.5 Hz (anomalous; trans).

cis- and trans-7,8-Dehydro-1-acetoxy-2-oxa-4-decalone (101A) and (101B). cis-7,8-dehydro-1-ol-2-oxa-4-decalone 87 (320 mg, 1.9 mmol) prepared by the method of Jones,[71] was added to a 0°C solution contining anhydrous pyridine (7 mL) and Ac_2O (3.5 mL). The solution was allowed to warm to room temperature and stirred magnetically for 12 h. After this time the solution was poured into 300 mL of 1N HCl (0°C) and extracted with $CHCl_3$ (6 x 35 mL). The combined organics were dried and the solution filtered. Removal of the solvent in vacuo gave a dark liquid which was eluted through 50 g of silica gel (EtOAc solvent system, 250 mL). The filtrate was evaporated to a pale yellow liquid. The residue was dissolved in 1.0 mL of $CHCl_3$ and purified by PLC in EtOAc-hexane (1:4). The non-UV absorbing band was eluted with 25 mL of CH_2Cl_2 and the solvent removed in vacuo

to give 101A+B (R_f 0.40) as a pale yellow oil, 280 mg, 88% yield. ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H, OCH_3), 2.17 (s, 3H, OCH_3), ca. 2.20-2.60 (m, 5H), 4.22 (m, 2H, CCH_2O), 5.73 (br, 2H, vinyl protons), 6.0 (d, 1H, J = 8 Hz, acetal proton), 6.08 (d, 1H, J = 3 Hz, acetal proton); MS, m/e (rel intens) 179 (3), 149 (2), 108 (18), 71 (100).

Epimerization of cis-7,8-dehydro-1-acetoxy-2-oxa-4-decalone (101A+B). cis-7,8-Dehydro-1-acetoxy-2-oxa-4-decalone 101A+B (120 mg, 0.71 mmol) was subjected to the epimerizing conditions given for 41A. After filtration through acidic ion exchange resin, the exchange resin was washed with an equal volume of MeOH (20 mL) and the combined filtrates evaported *in vacuo* to give 87B, 117 mg, a yield of 92%. The epimerized hemiacetal 87B was re-acetylated by the method given above to afford 102A+B, a pale yellow oil (R_f 0.40, 85 mg), for a yield of 59%.

GC-mass spectrometric analysis of cis- and trans-7,8-dehydro-1-acetoxy-2-oxa-4-decalone (101) and (102). To analyze the epimeric mixtures of 101A+B and 102A+B a Dupont 21-491 B mass spectrometer interfaced to a Varian 2740 GC and Nova 2 data system was used. A 1% OV 17, 100/120 Varaport 30 column (6 foot x 2 mm ID) was used, with a carrier gas flow rate of 30 cc N^2/minute. Co-injection of 101A+B and 102A+B gave four GC peaks with corresponding mass spectra. The retention times, fragmentation patterns and relative intensities are detailed below. MS, m/e (rel intens);

Peak A (102A or B): (ret time, 7.04 min) 184 (1) 183 (1),

183 (1), 152 (2), 151 (2), 123 (6), 126 (6), 121 (5).

Peak B (102A or B): (ret time, 8.30 min) 210, M^+ (10), 184 (1), 183 (2), 132 (1), 152 (1), 151 (1), 123 (8), 122 (6), 121 (7), 98 (2), 97 (1), 71 (3), 69 (2).

Peak C (101A or B): (ret time, 12.30 min) 210 M^+ (0.5), 184 (1), 183 (2), 151 (3), 122 (5), 96 (1), 71 (1), 68 (2).

Peak D (101A or B): (ret time, 13.04 min) 210 M^+ (0.5), 183 (0.5), 151 (8), 122 (4), 96 (6), 68 (2).

cis-7,8-Dehydro-1-methoxy-2-oxadecalin-4-carbonitrile (98) by the tosylmethyl isocyanide method. Our experience with the tosylmethyl isocyanide reagent (TOSMIC) has shown that this is a capricious reaction and one that can only be controlled by carefully defined experimental procedures.

TOSMIC, as it comes from Aldrich Chemical Co., Inc., has been found by myself and others to contain as much as 30% impurities.[97] These impurities are deleterious and must be eliminated if present. Purification of this reagent may be accomplished in the following manner. TOSMIC (5.0 g, 0.026 mol) was dissolved in 50 mL of anhydrous MeOH, at room temperature, and one-half of the solvent removed by rotary evaporation *in vacuo* at 35°C. Crystallization occurred rapidly and the mother liquor was filtered off and saved for recovery of additional crops of crystals. The first crop of crystals was collected quickly and dissolved in 20 mL of CH_2Cl_2. This solution

was suction filtered through a pad of neutral alumina (9.0 g). After the primary filtration, the filter pad was washed with CH_2Cl_2 (8 x 15 mL) to remove the last traces of TOSMIC. Rotary evaporation of the solvent led to the formation of a white, plate-like solid which was broken up and dried by vacuum desiccation on the high vacuum line for 6.0 h at 25°C. The weight of recovered solid was 3.43 g (68% yield); mp 114°-115°C (lit.[98] mp 114-116°C).

Cis-7,8-Dehydro-2-oxa-4-decalone 41A (1.34 g, 7.4 mmol), purified TOSMIC (1.575 g, 1.1 equiv), 1,2-dimethoxyethane (70 mL, must be freshly distilled over CaH or $LiAlH_4$) and 0.5 mL of anhydrous MeOH (2 equiv, relative to TOSMIC) were added to a dry, 250 mL round bottom flask equipped with a stirring bar and flushed with N_2. After cooling the flask to 0-5°C with a water ice-bath, solid KO*t*-Bu (1.814 g, 2 equiv, relative to TOSMIC) was quickly added to the stirred solution. The reaction immediately turned a bright, rusty red and was stirred at 0-5°C for one additional hour. At this time TLC (EtOAc-hexane, 1:3) showed one major non-UV absorbing spot (R_f 0.67). If this reaction mixture was then allowed to warm to room temperature for 15 min, a second spot forms with a higher R_f (0.78). If the solution was warmed for 15 min more at 40°C, the lower R_f spot disappeared. This particular reaction was warmed to 22°C and allowed to stir for an additional 30 min. The reaction mixture was then quenched with 20% HOAc (0.25 mL). The pH of the solution dropped to 6.5 (test paper), the treatment with dilute acid

having solubilized the precipitated salts to form a brownish liquid. Then, 90% of the solvent was removed *in vacuo*. CH_2Cl_2 (75 mL) was added to remove the soluble material from the reaction flask, the reaction flask was then washed with H_2O (40 mL), and the organic and inorganic solutions combined in a 250 mL separatory funnel. The aqueous phase was extracted with more CH_2Cl_2 (2 x 75 mL) and the combined organics washed with $NaHCO_3$ solution (50 mL) and dried. After filtration, most of the solvent was removed *in vacuo* and the yellowish concentrate (1.6 mL) put onto a 40 x 2 cm silica gel column and eluted with an Et_2O hexane, 1:1, solvent system. The fractions containing the desired product were evaporated *in vacuo* to give **98A** (215 mg, R_f 0.78), **98B** (644 mg, R_f 0.67), and a mixed fraction of **98A** and **98B** (69 mg); yield, 67% (yields were found to vary from 40-75%).[98]

98A: IR ($CHCl_3$) ν 2242 (CN), 1600 (C=C), 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ *ca.* 2.30-3.00 (m, 7H), 3.39 (s, 3H, OCH_3), 3.88 (d, 2H, *J* = 8 Hz, CCH_2O), 4.42 (s, 1H, acetal proton), 5.67 (s, 2H, vinyl proton); MS, *m/e* (rel intens) 193, M^+ (22), 161 (16), 138 (8), 80 (100).

Anal. Calcd for $C_{11}H_{15}O_2N$: C, 68.36; H, 7.82; N, 7.25. Found: C, 68.28; H, 7.52; N, 6.91.

98B: IR (film) ν 2900, 2830, 2240 (CN), 1650 (C=C), 1435 cm^{-1}; ^1H NMR ($CDCl_3$) δ *ca.* 1.85-2.60 (m, 6H), 2.82 (q, 1H, *J* = 5 Hz, CHCN); 3.44 (s, 3H, OCH_3), 3.97 (q of d, 2H, *J* = 18 and 6 Hz, CCH_2O), 4.43

(d, 1H, J = 5 Hz, acetal proton), 5.73 (s, 2H, vinyl protons); MS, m/e (rel intens) 193, M^+ (22), 161 (24), 132 (20), 113 (50), 80 (100).

270 MHz ^{1}H NMR analysis of the relative stereochemistry of cis-7,8-dehydro-1-methoxy-2-oxadecalin-4-carbonitrile (98A) and (98B). The epimeric nitriles 98A and 98B were analyzed by 270 MHz ^{1}H NMR ($CDCl_3$) in the manner previously explained for one-half band width measurements ($\Delta\nu^{1/2}$).

Decoupling data located the H-1, H-4, H-5, and H-10 resonances and enabled us to determine the approximate coupling constants of these signals;

98A (18 Hz cm)

Proton observed	J ($\Delta\nu^{1/2}$)	ΔJ ($\Delta\nu^{1/2}$)	Proton irradiated
H-1, 3.85 ppm	ca. 6.4-6.6 Hz	no change	H-10
H-4, 2.82	30.5-30.7	ca. 8.9-9.1 Hz	H-5
H-5, 2.47	25.2-25.4	no change	H-1
H-5	25.2-25.4	8.9-9.1	H-4
H-5	25.2-25.4	3.5-3.7	H-10
H-10, 2.28	19.7-19.9	no change	H-1
H-10	19.7-19.9	3.5-3.7	H-5

By aliphatic Karplus equation and Drieding models: Θ H-4, H-5 = ca. 140° = 8.9-9.1 Hz (trans).

Θ H-5, H-10 = ca. 65° = 3.5-3.7 Hz (cis).

98B (18 Hz cm)

Proton observed	J ($\Delta\nu^{1/2}$)	ΔJ ($\Delta\nu^{1/2}$)	Proton irradiated
H-1, 4.40 ppm	ca. 11.6-11.8 Hz	ca. 5.8-6.1 Hz	H-10
H-4, 2.13	16.1-16.3	3.5-3.7	H-5
H-5, 1.77	34.1-34.3	no change	H-1
H-5	34.1-34.3	3.5-3.7	H-4
H-5	34.1-34.3	3.5-3.7	H-10
H-10, 1.23	19.7-19.9	5.8-6.1	H-1
H-10	19.7-19.9	4.0-4.2	H-5

By aliphatic Karplus equation and Drieding models: Θ H-1, H-10 = ca. 130° = 5.8-6.1 Hz (trans).

Θ H-4, H-5 = ca. 65° = 3.5-3.7 Hz. (cis).

Θ H-5, H-10 = ca. 65° = 3.7-4.0 Hz (cis).

cis-7,8-Dehydro-1-methoxy-2-oxadecalin-4-carboxylic acid amide (99). To a 50 mL round bottom flask, equipped with a stirring bar and reflux condenser were added cis-7,8-dehydro-1-methoxy-2-oxadecalin-4-carbonitrile 98A+B (611 mg. 3.2 mmol), EtOH (15 mL, 100% commerical), H_2O_2 (30%, 3 mL) and NaOH solution (6N, 0.3 mL). The resulting pH of the reaction mixture was ca. 7.6. The reaction mixture was refluxed at 75-90°C, the pH being monitered every 10 min. When the pH dropped below 7.5, enough 6N NaOH was added to raise the pH to about 8.0. After 2.0 h, TLC indicated that the reaction was

about 95% completed. The peroxides were reduced by addition of a saturated aqueous solution of $Na_2S_2O_3$ (15 mL) and the reaction mixture was reduced to one-third of its volume by rotary evaporation *in vacuo*. The resulting mixture was mixed with CH_2Cl_2 (30 mL) and transferred to a 125 mL separatory funnel. Another 30 mL of CH_2Cl_2 was added, and the solution was washed with saturated NaCl solution (25 mL). The brine was extracted with CH_2Cl_2 (3 x 80 mL) and the combined organics dried. After filtration, the solvent was removed *in vacuo* to give only **99** (548 mg, 81%) as a white solid.[87] The crude material was recrystallized from MeOH to give long, clear spar- crystals; mp 200-204°C; TLC (EtOAc-hexane, 1:1) R_f = 0.33; IR ($CHCl_3$) ν 3520 (NH_2), 3405 (NH_2), 2900, 1680 (C=O), 1588 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ *ca.* 1.7 (br, 1H), *ca.* 2.1 (s, 4H), *ca.* 2.3 (br, 2H), 3.40 (s, 3H, OCH_3), 3.88 (d, 2H, *J* = 8 Hz, CCH_2O), 4.40 (s, 1H, acetal proton), 5.63 (s, 2H, vinyl protons); MS, *m/e* (rel intens) 211 M^+, (10), 191 (9), 189 (14), 179 (40), 72 (100).

Anal. Calcd for $C_{11}H_{17}O_3N$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.90; H, 8.51; N, 6.46.

cis-7,8-Dehydro-1-methoxy-2-oxadecalin-4-carboxylic acid hydrazide (105). *cis*-7,8-Dehydro-1-methoxy-2-oxadecalin-4-carboxylic acid amide, **99** (200 mg, 0.95 mmol), was mixed with hydrazine hydrate (6 mL, 99%) and poured into a 20 mL, thick walled, Pyrex tube equipped with a stirring bar. After sealing the tube under vacuum, it was refluxed for 36 h in an oil bath at 160°C. After

opening the tube, TLC (EtOAc-EtOH, 8:1) indicated that there was a 90% conversion of 99 to 105.[88] The solvent was removed by rotary evaporation in vacuo at 75°C, and the residue was dissolved into $CHCl_3$ (60 mL). This solution was transferred to a 125-mL separatory funnel and washed with brine (40 mL). The brine was then back extracted with CH_2Cl_2 (2 x 50 mL), and the organics were combined and dried. After filtration, removal of the solvent gave 105 (176 mg, 82%) as a pale, glassy liquid; TLC (EtOAc-EtOH, 8:1) R_f = 0.50; IR ($CHCl_3$) ν 3440 (NH), 3320 (NH), 2959, 1668 (C=O), 1620 (C=C), 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ ca. 1.80-2.90 (m, 9H), 3.48 (s, 3H, OCH_3), 4.03 (d, 2H, J = 7 Hz, CCH_2O), 5.49 (s, 1H, $NHNH_2$), 5.65 (s, 2H, vinyl protons); MS, m/e (rel intens) 210 (7), 194 (100), 179 (12), 163 (22), 69 (100).

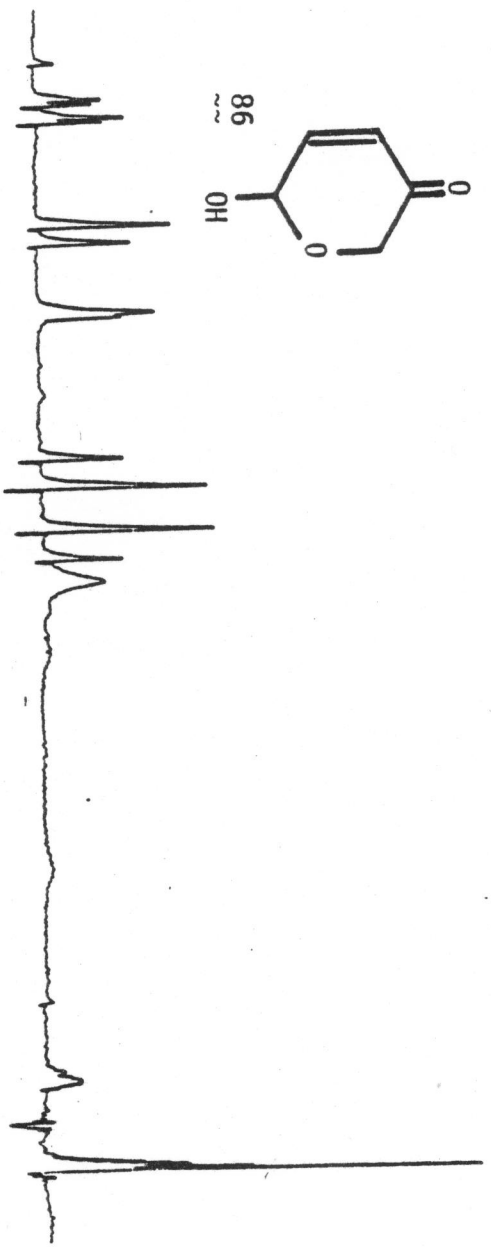
Anal. Calcd for $C_{11}H_{18}O_3N_2$: C, 58.39; H, 8.02. Found: C, 58.06; H, 7.87.

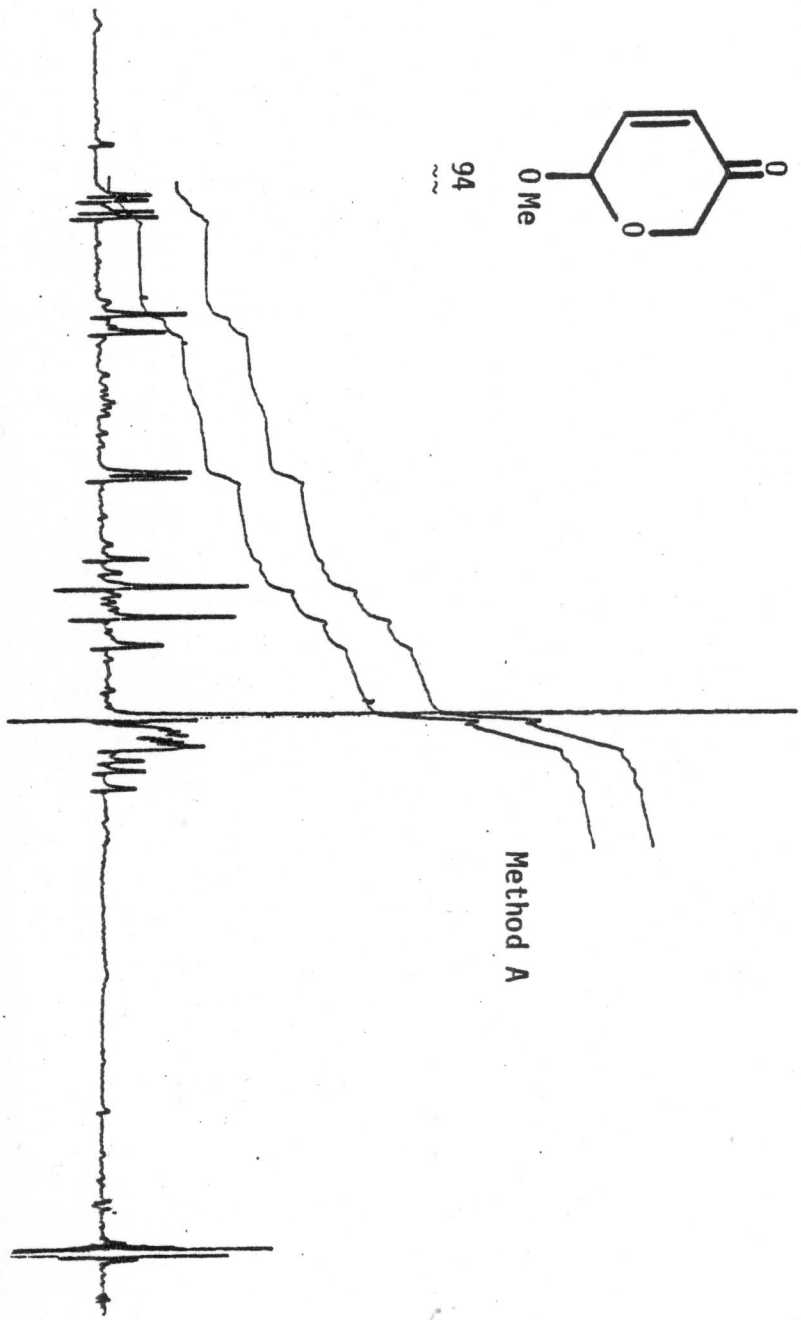
cis-7,8-Dehydro-1-methoxy-2-oxadecalin-4-carboxylic acid methyl ester (7A). Freshly cut sodium metal (60 mg, 0.0024 g atom) was added to anhydrous MeOH (35 mL) in a dry, 100-mL, two necked flask equipped with a stirring bar and protected by a N_2 atmosphere. Freshly prepared Cu(I)Cl (240 mg, 2.4 mmol) was added to the mixture after complete solubilization of the sodium. The solution immediately turned blue.[101] This solution was stirred for about 5.0 min and a bubbler, connected to an oxygen tank, was inserted through the vertical neck of the flask. Into the side neck of the

flask was placed a 25 mL pressure equalizing dropping funnel charged with 105 (333 mg, 1.47 mmol) dissolved in anhydrous methanol (15 mL). This solution was dripped into the reaction flask over a 30 min period, during which time the vessel was well stirred and a vigorous stream of O_2 bubbled through it. After the addition, the reaction flask was swept with O_2 for 1.0 h more. The solvent was removed from the reaction flask *in vacuo* and the resulting residue was dissolved in Et_2O (75 mL). This solution was poured into a 250 mL separatory funnel and washed with brine (80 mL). The brine solution was back extracted with Et_2O (2 x 60 mL) and the organics combined and dried. After filtration, most of the solvent was removed by rotary evaporation *in vacuo* and the concentrated solution put onto a 30 x 1.5 cm silica gel column and eluted with an Et_2O-hexane (1:3) solvent system. Evaporation of the fractions containing the product gave 7A (168 mg, 50%) as a clear glasslike material. Despite repeated attempts, 7A could not be recrystallized. TLC (Et_2O-hexane, 1:3) R_f = 0.85; IR ($CHCl_3$) ν 2900, 1725 (C=O), 1512, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (m, 4H), *ca.* 2.50-2.80 (m, 2H), 3.38 (s, 3H, OCH_3), 3.68 (s, 3H, CO_2CH_3), 3.78 (m, 2H, CCH_2O), 4.38 (s, 1H, acetal proton), 5.60 (s, 2H, vinyl proton); MS, *m/e* (rel intens) 226, M^+ (19), 211 (4), 194 (30), 164 (14), 79 (100).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 64.09; H, 8.17.

V. Spectra





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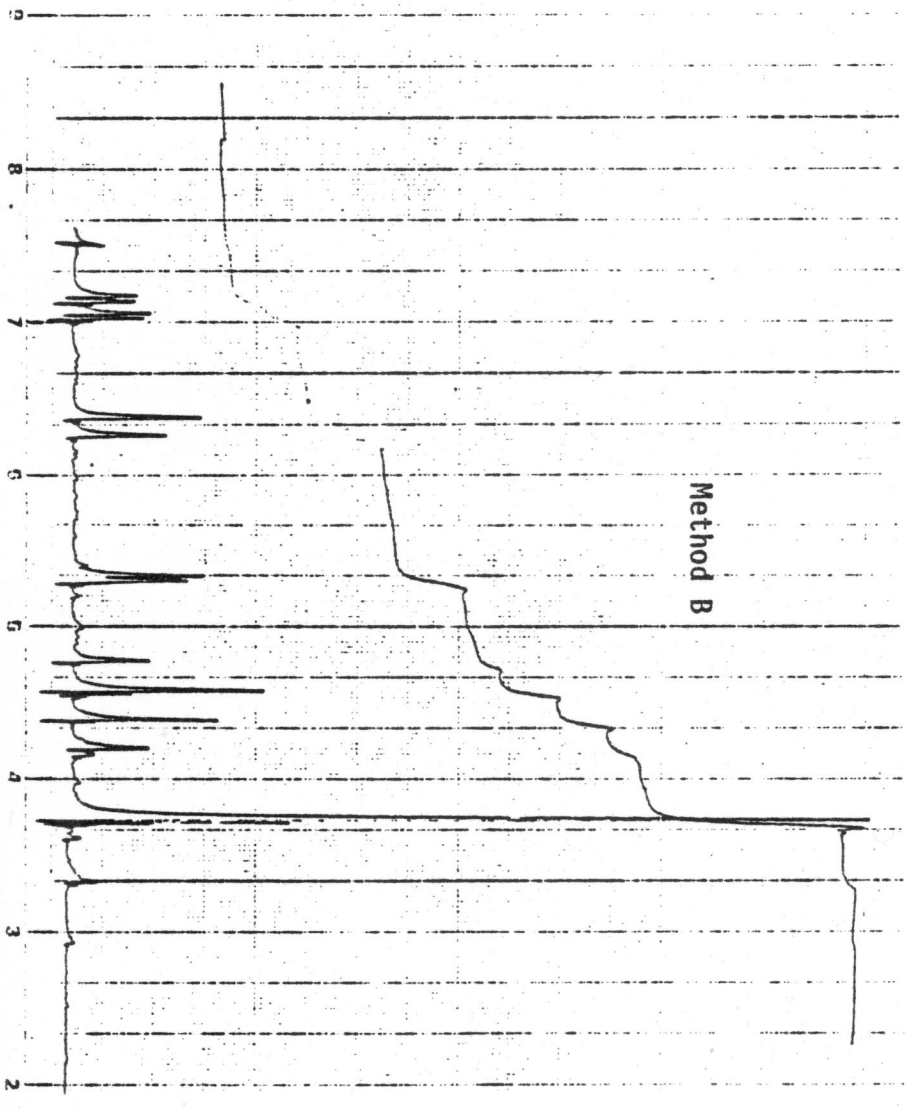
Method A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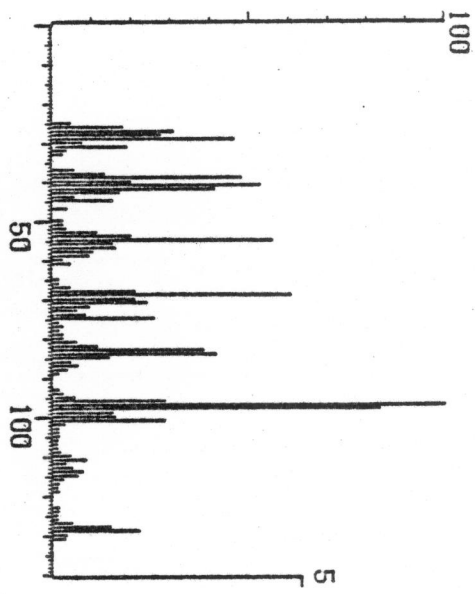
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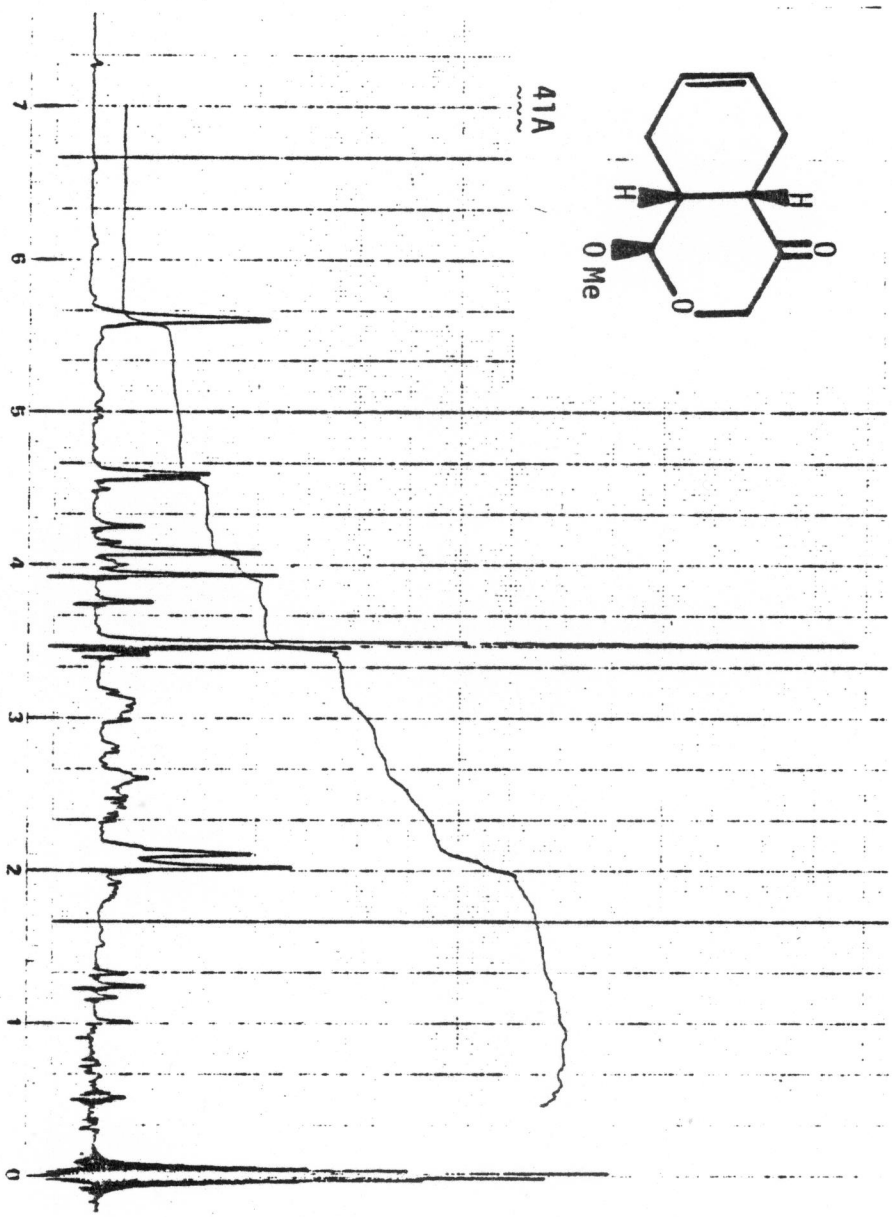
41A
H
H
O
O Me
O
0
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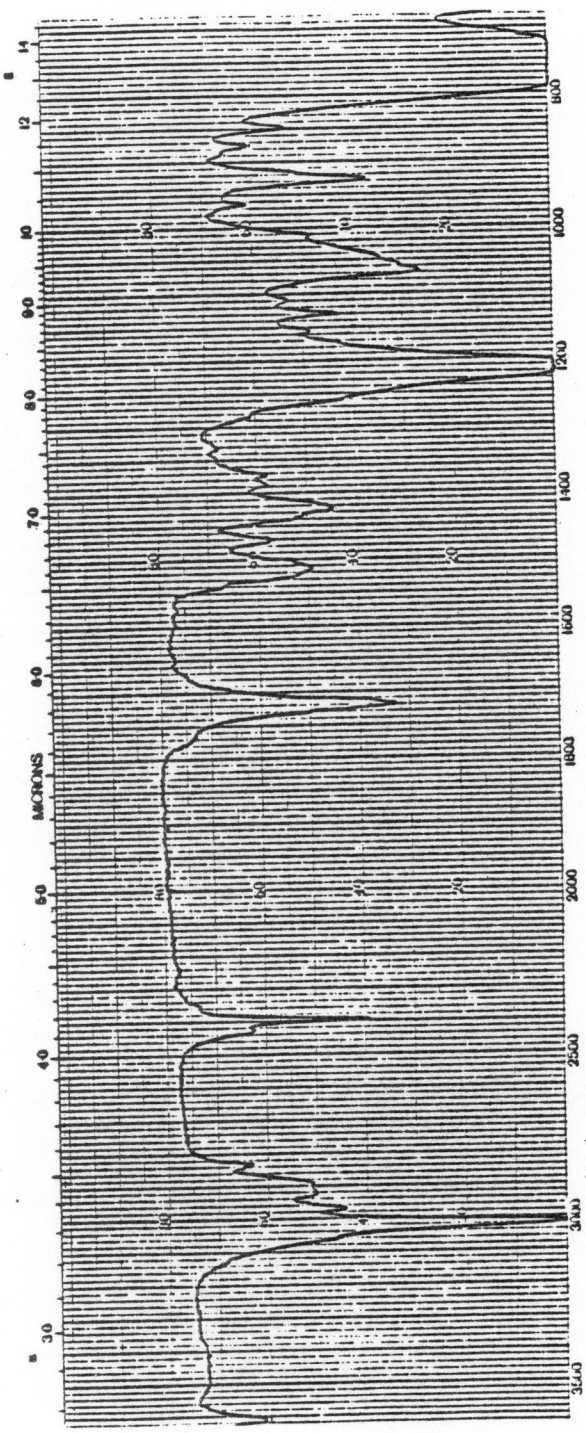
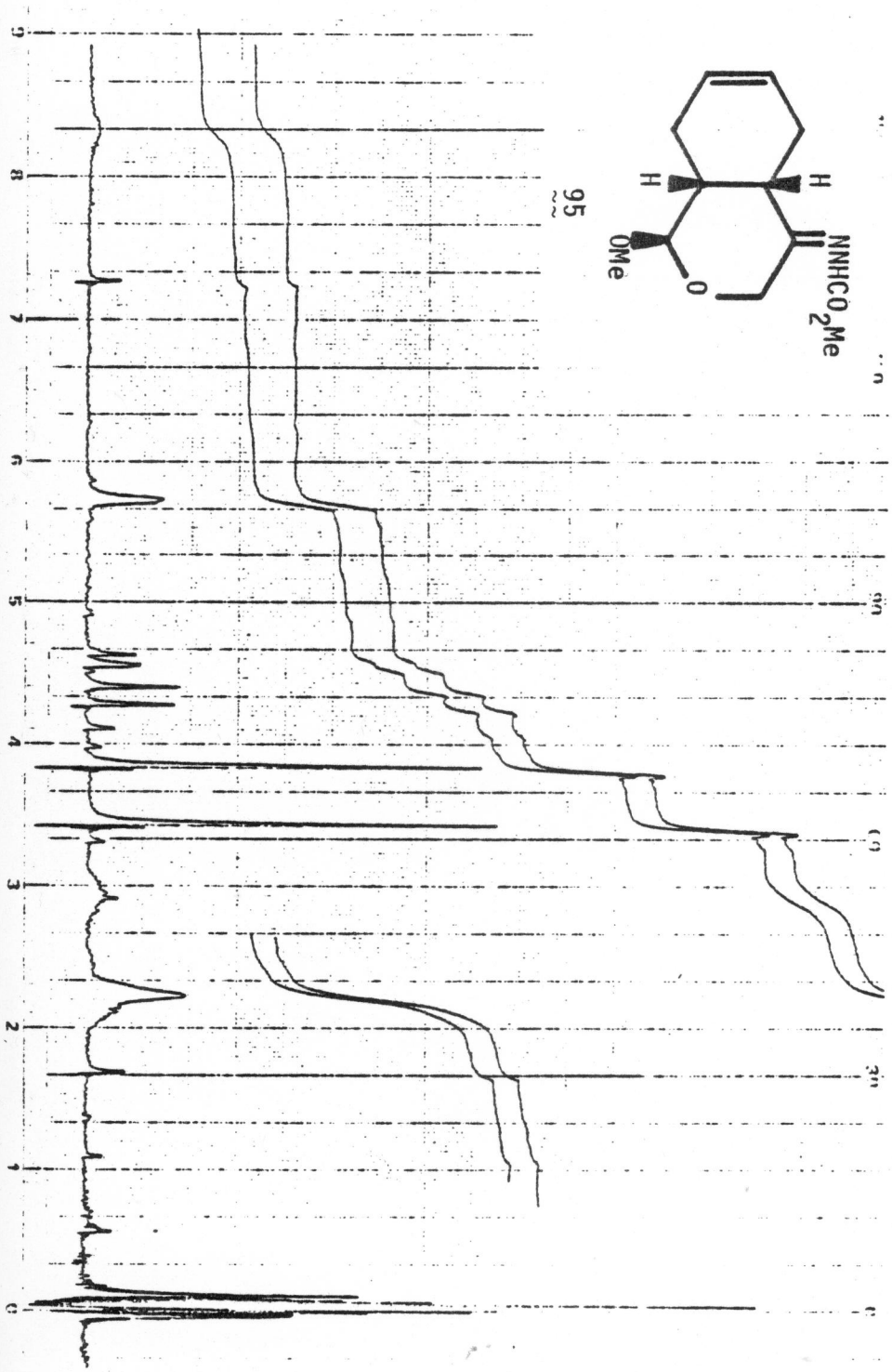
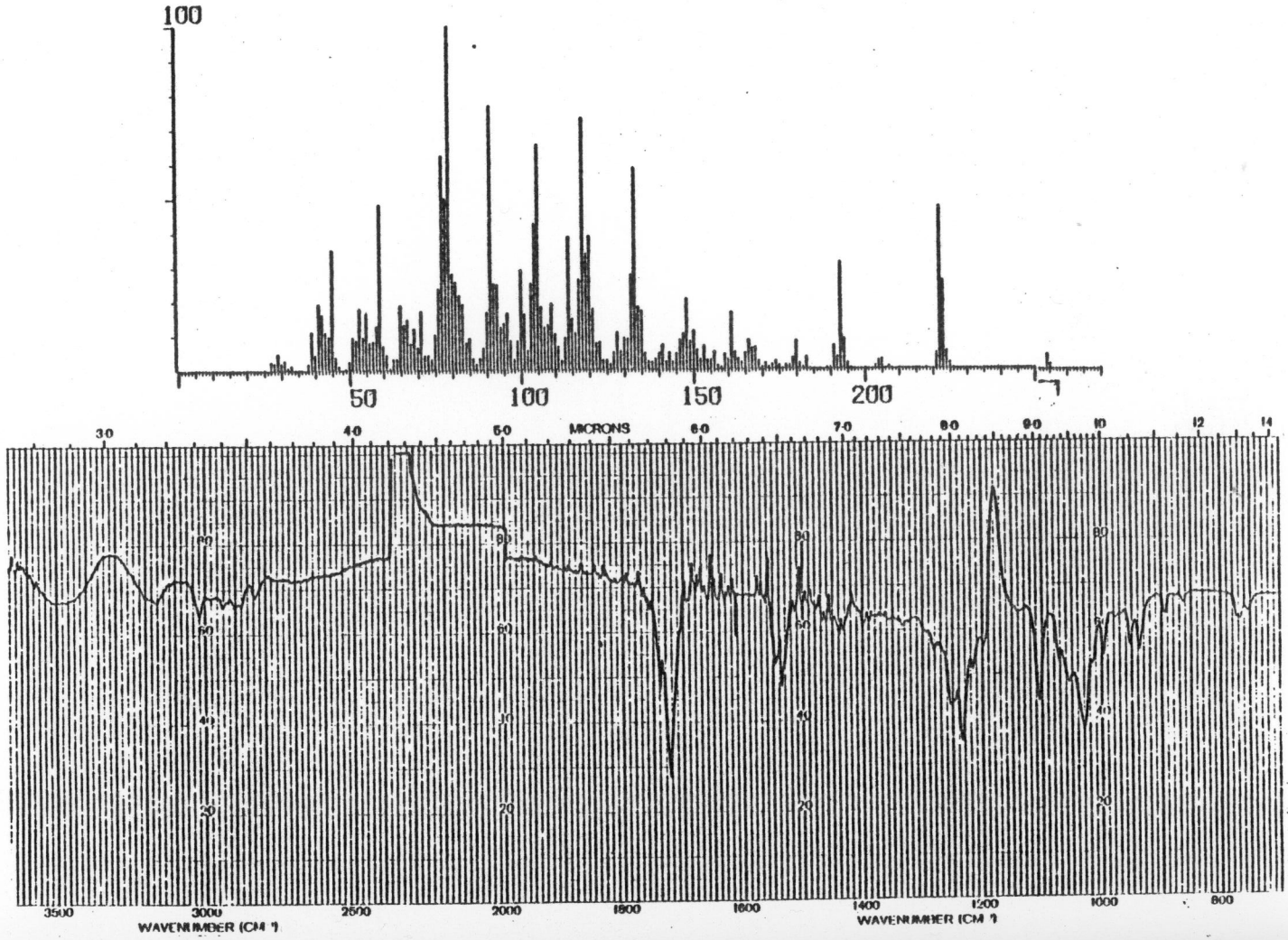
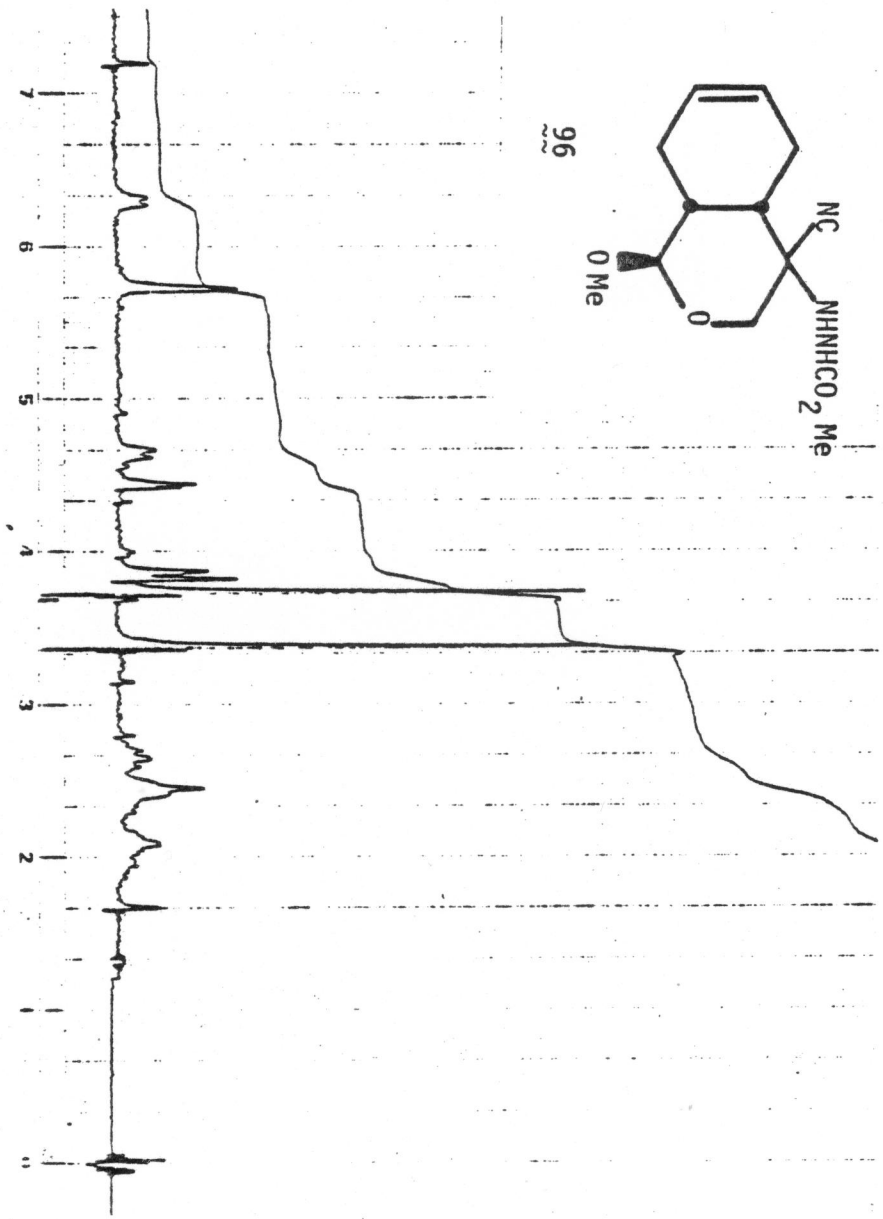
6
7

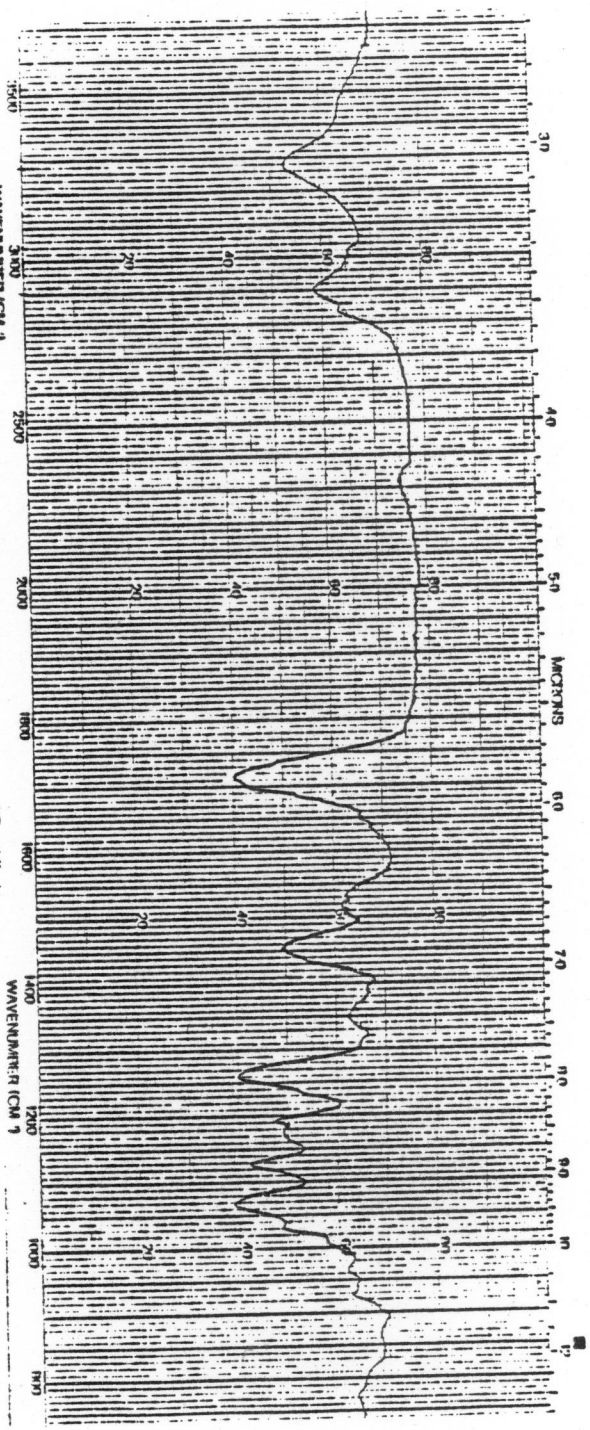

MICRONS
2
4
6
8
10
12
14
30
40
50
60
70
80
90
100
2500
2000
1800
1600
1400
1200
1000
800
3500
3000

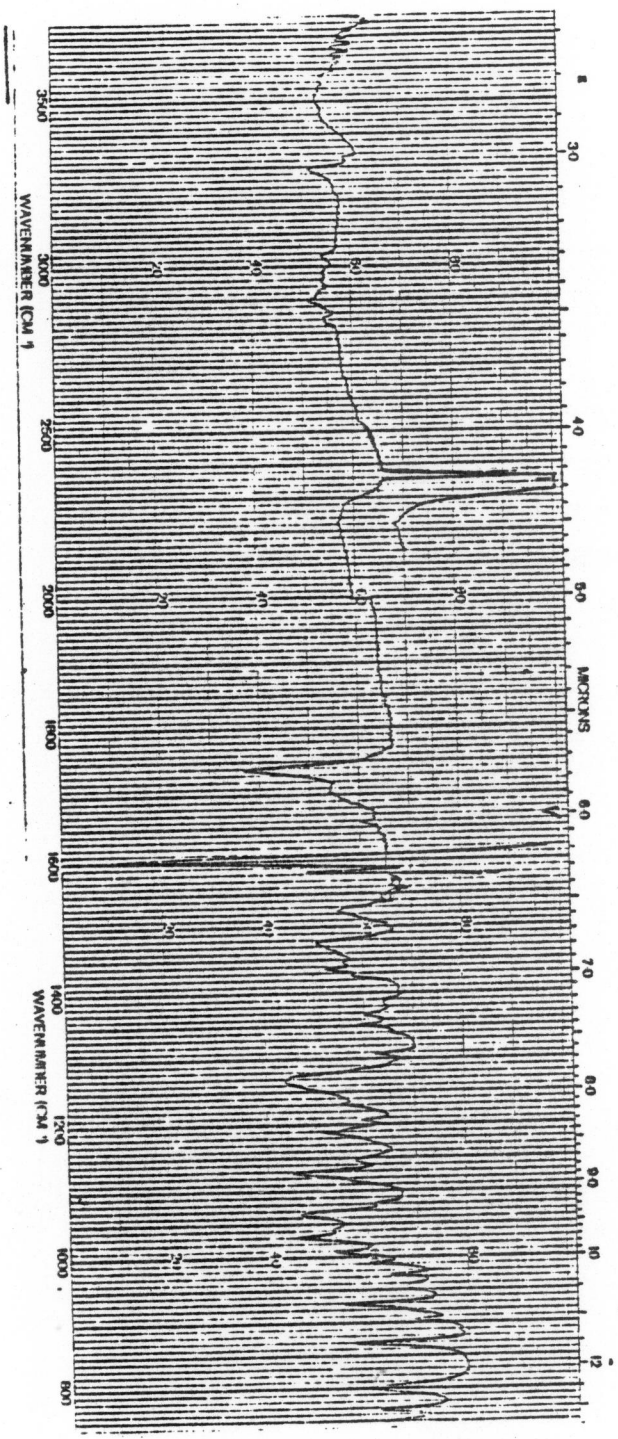


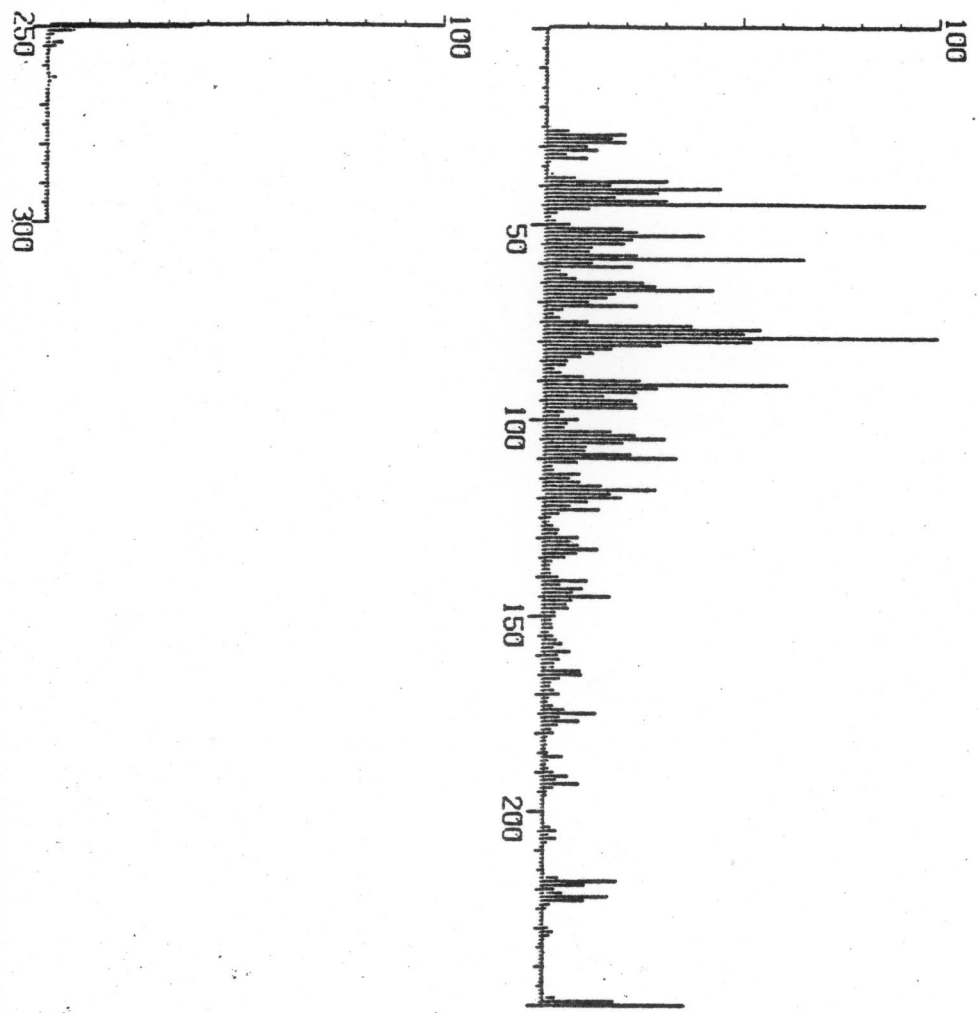
95

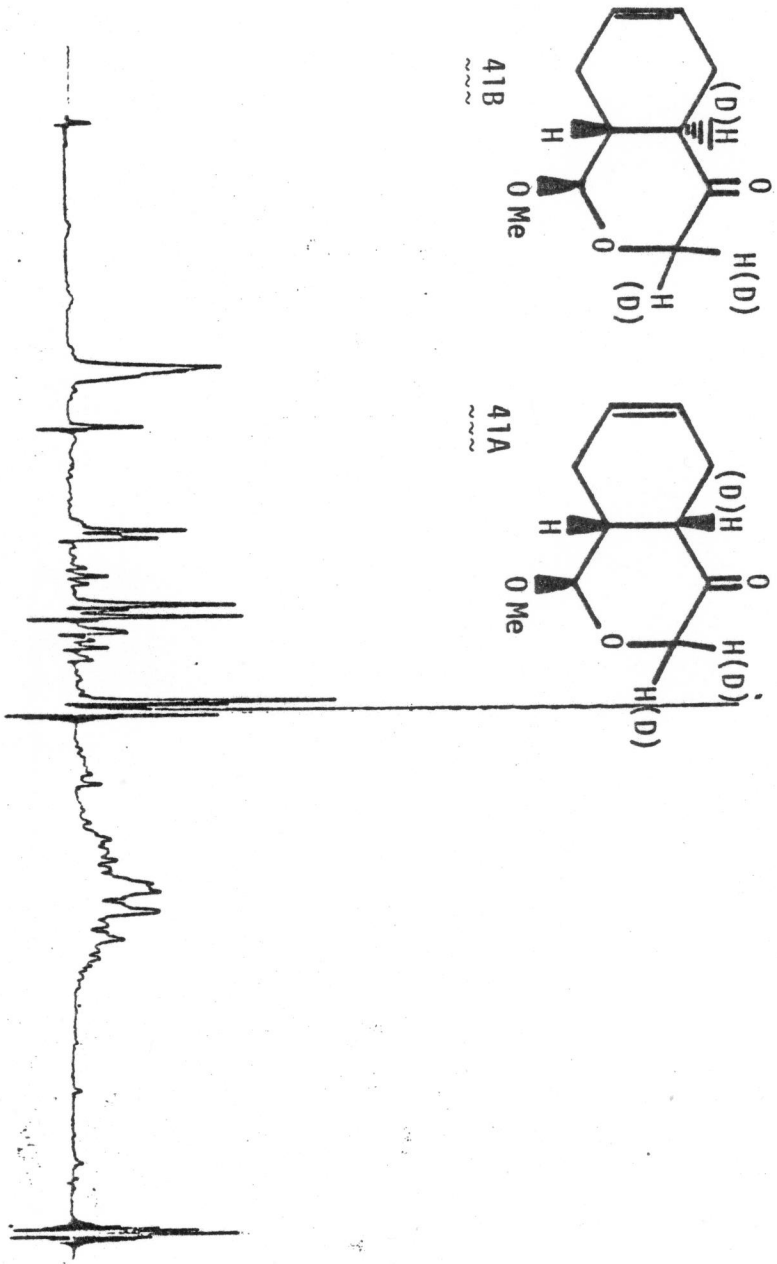

100
50
100
150
200
MICRONS
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)

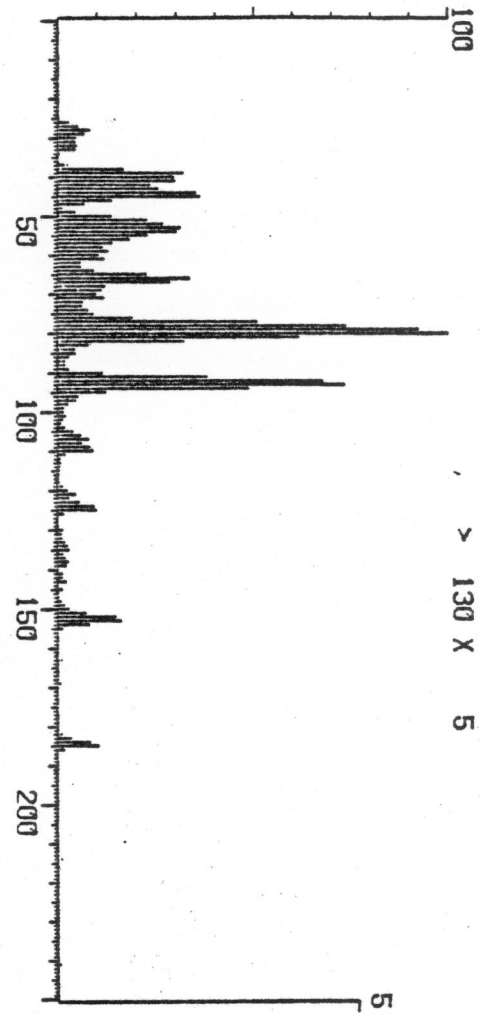

NC
NHNHCO2 Me
O Me
O
96

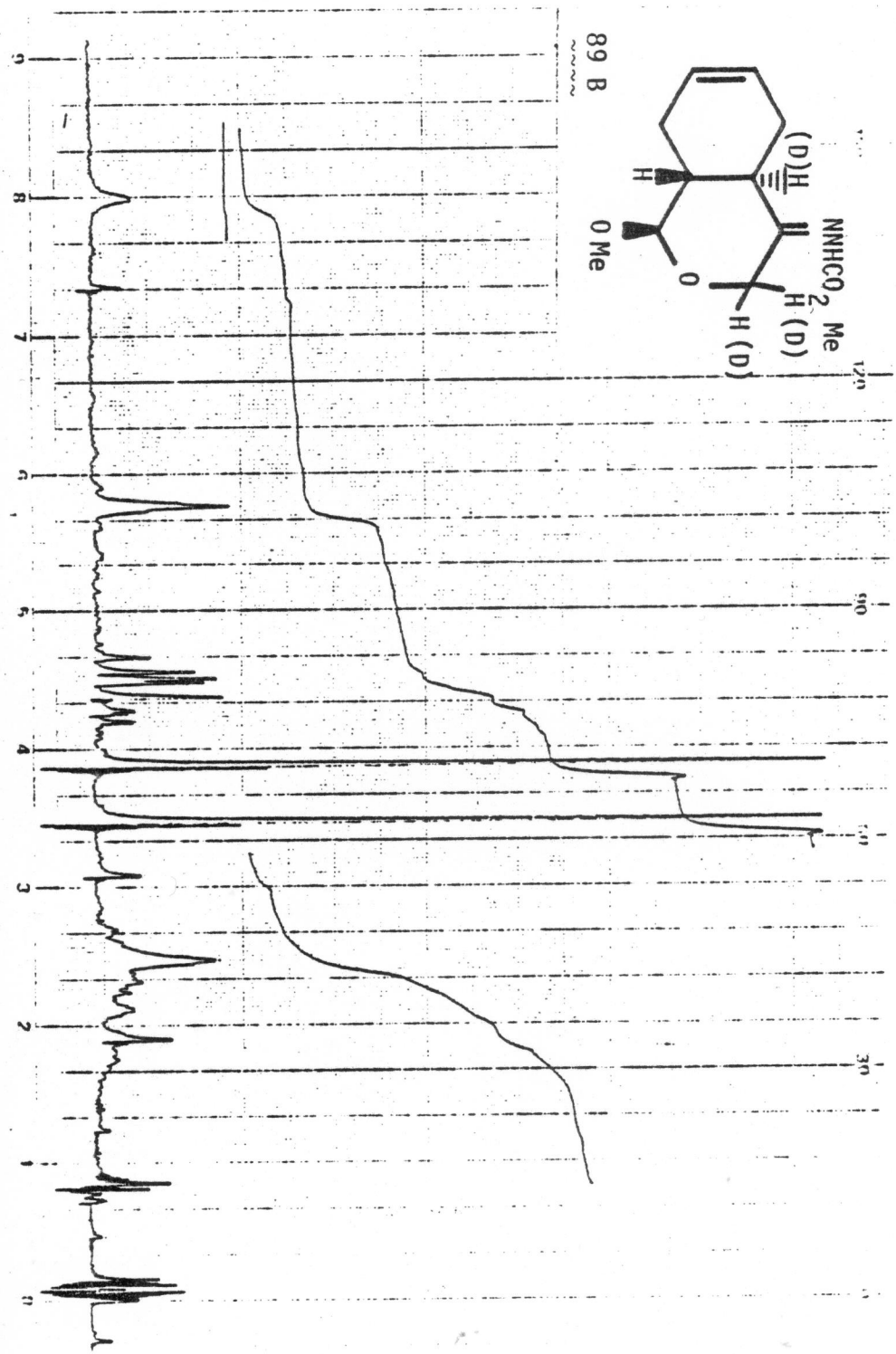

WAVENUMBER (CM-1)
MICRONS
WAVENUMBER (CM-1)

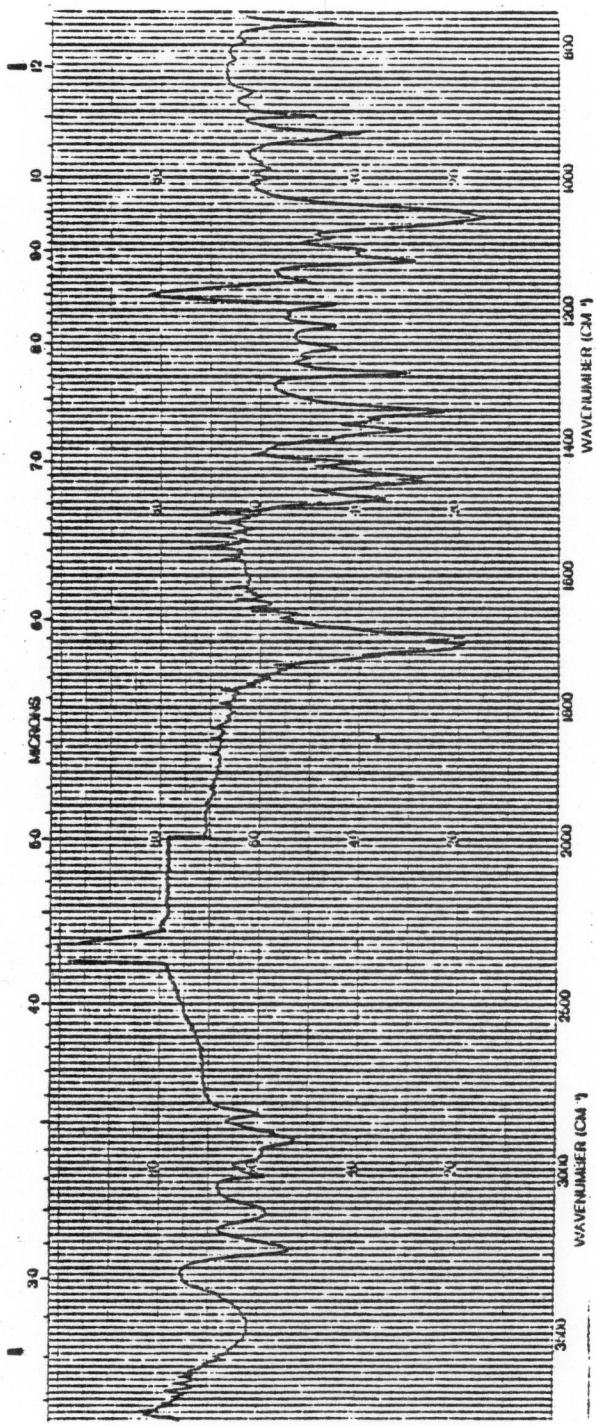

WAVENUMBER (CM-1)
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
MICRONS
2.5
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10
12

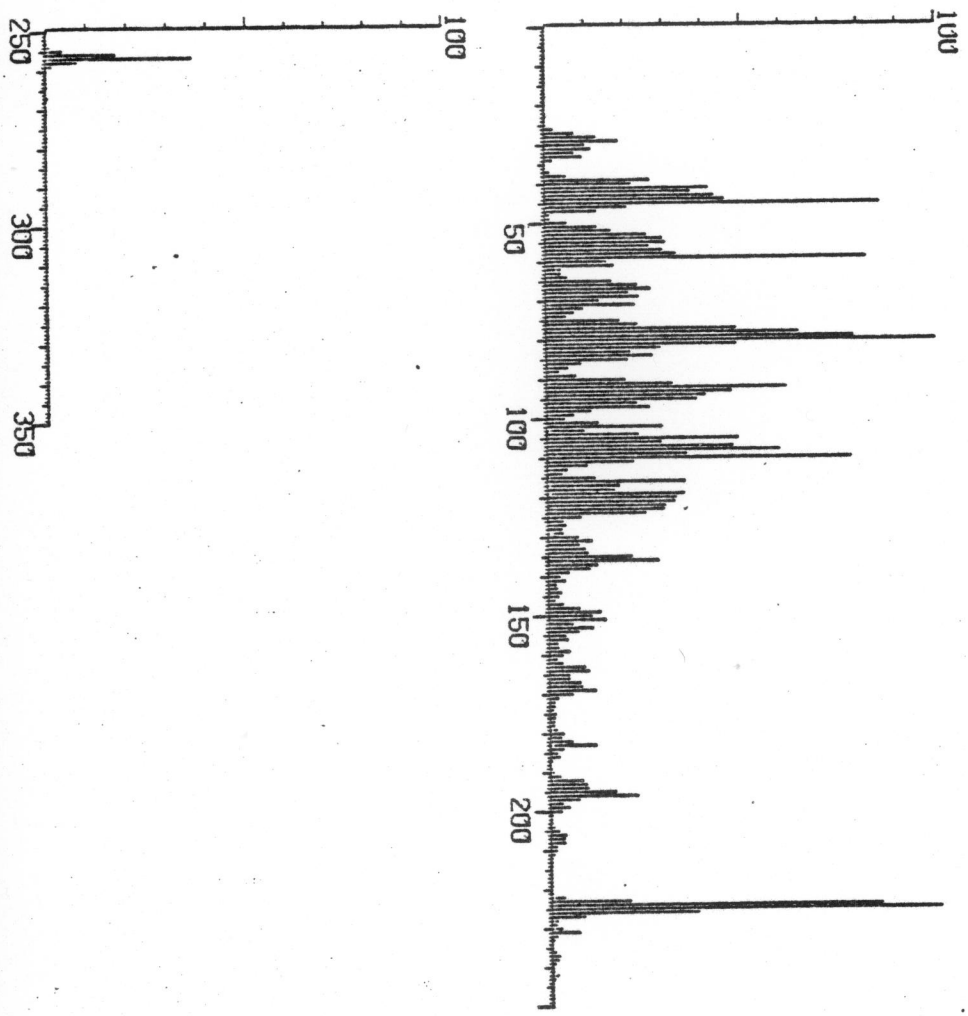

100
50
100
150
200
100
250
300


41B
41A
H
O Me
O
H(D)
(D)H
(D)

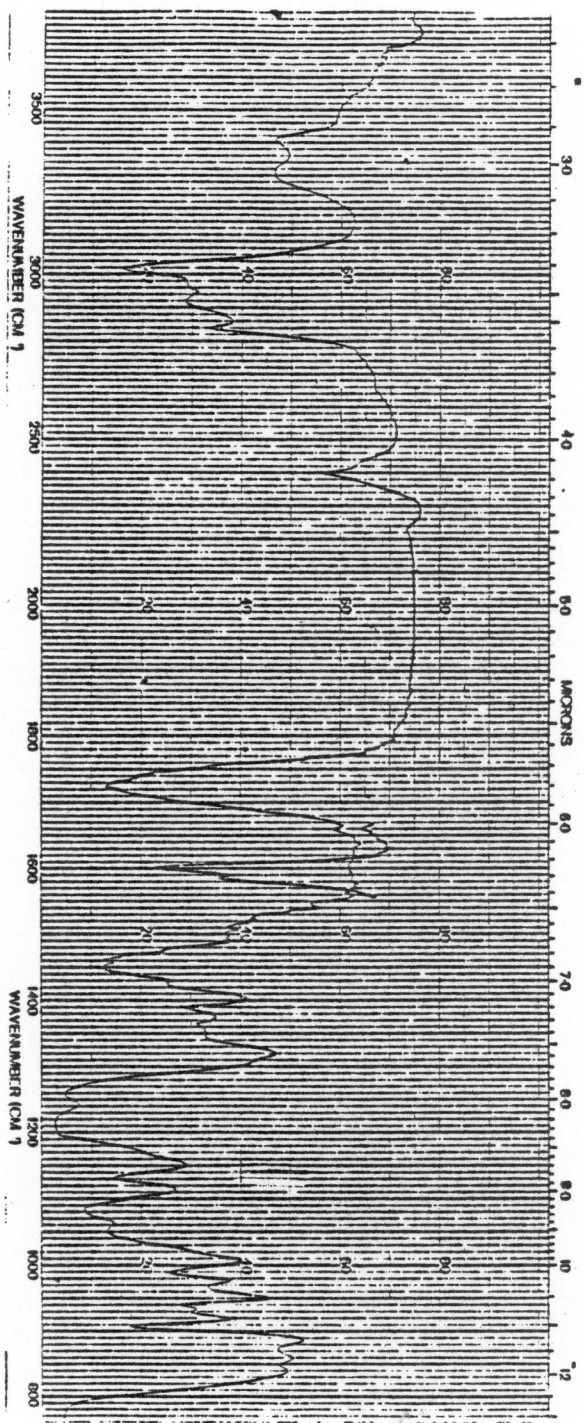

100
50
100
150
200
5
> 130 X 5

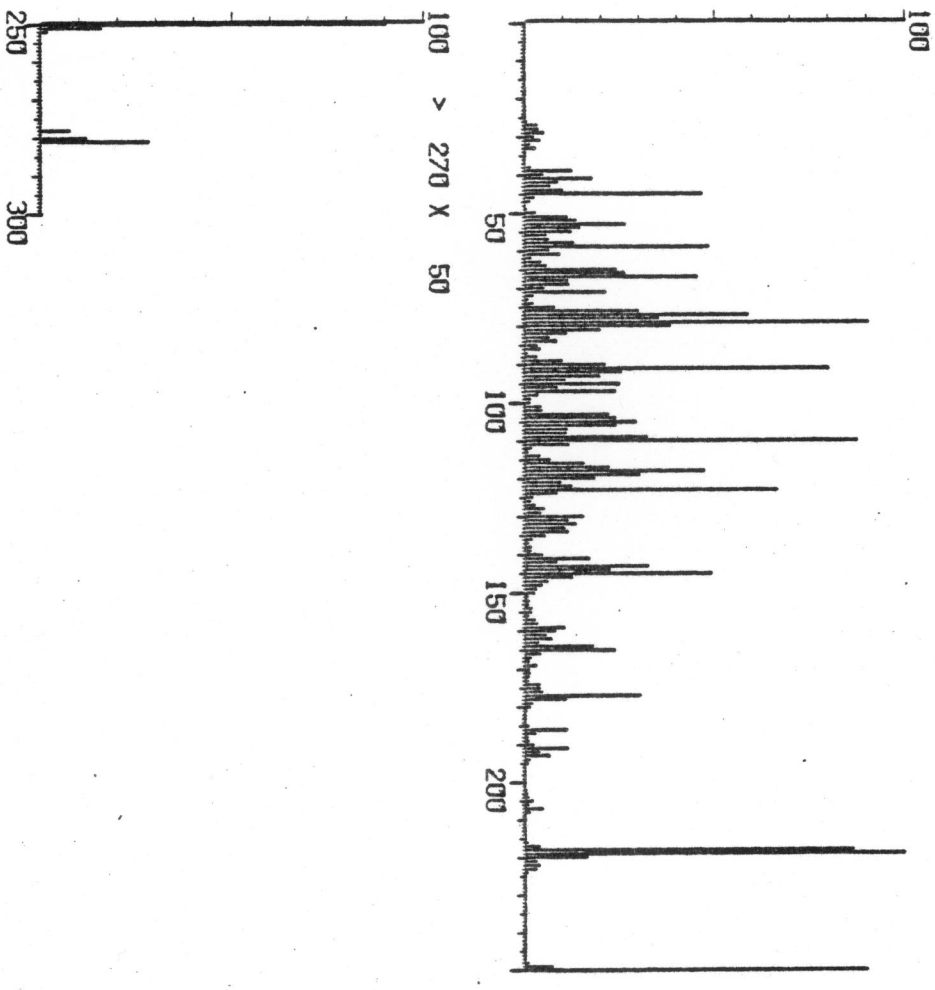

89 B
NNHCO2 Me
(D)H
H (D)
H (D)
H
O
O Me

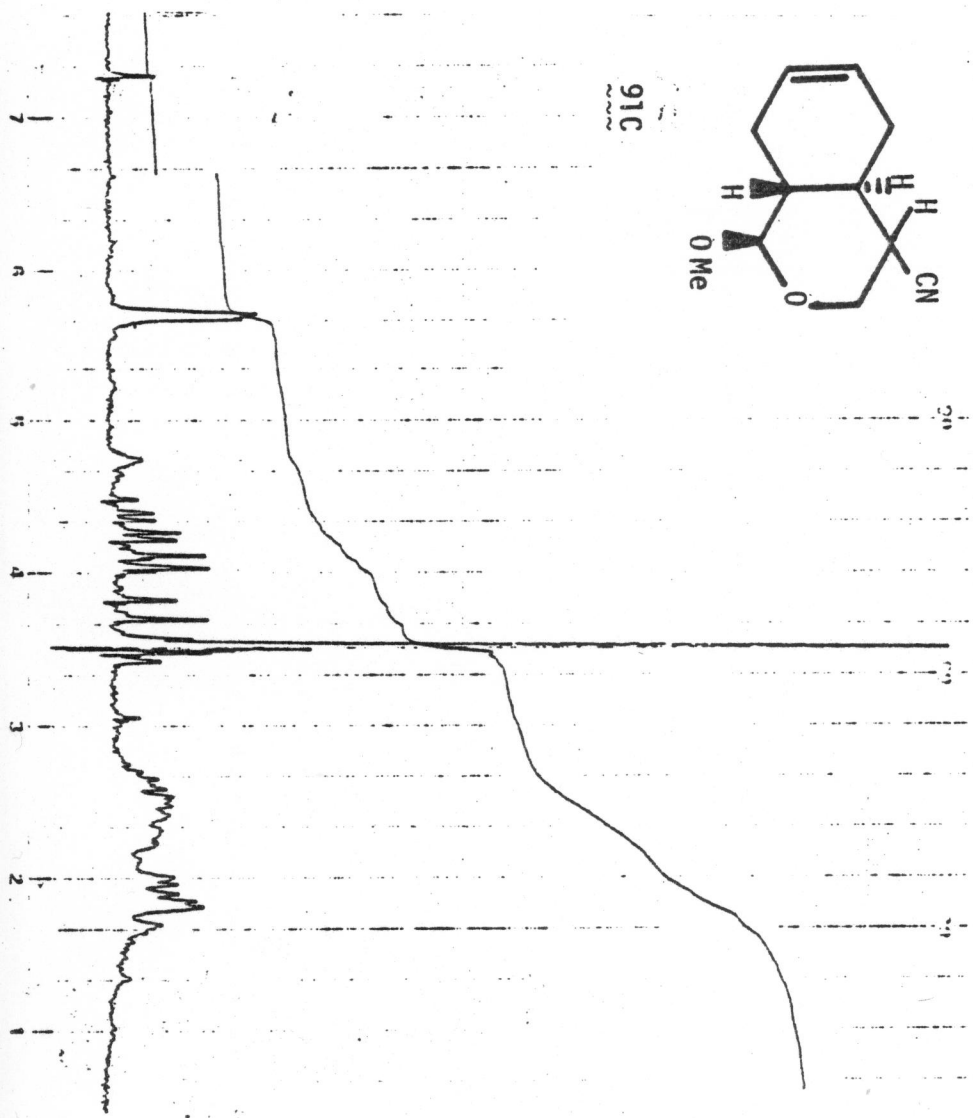

MICRONS
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)

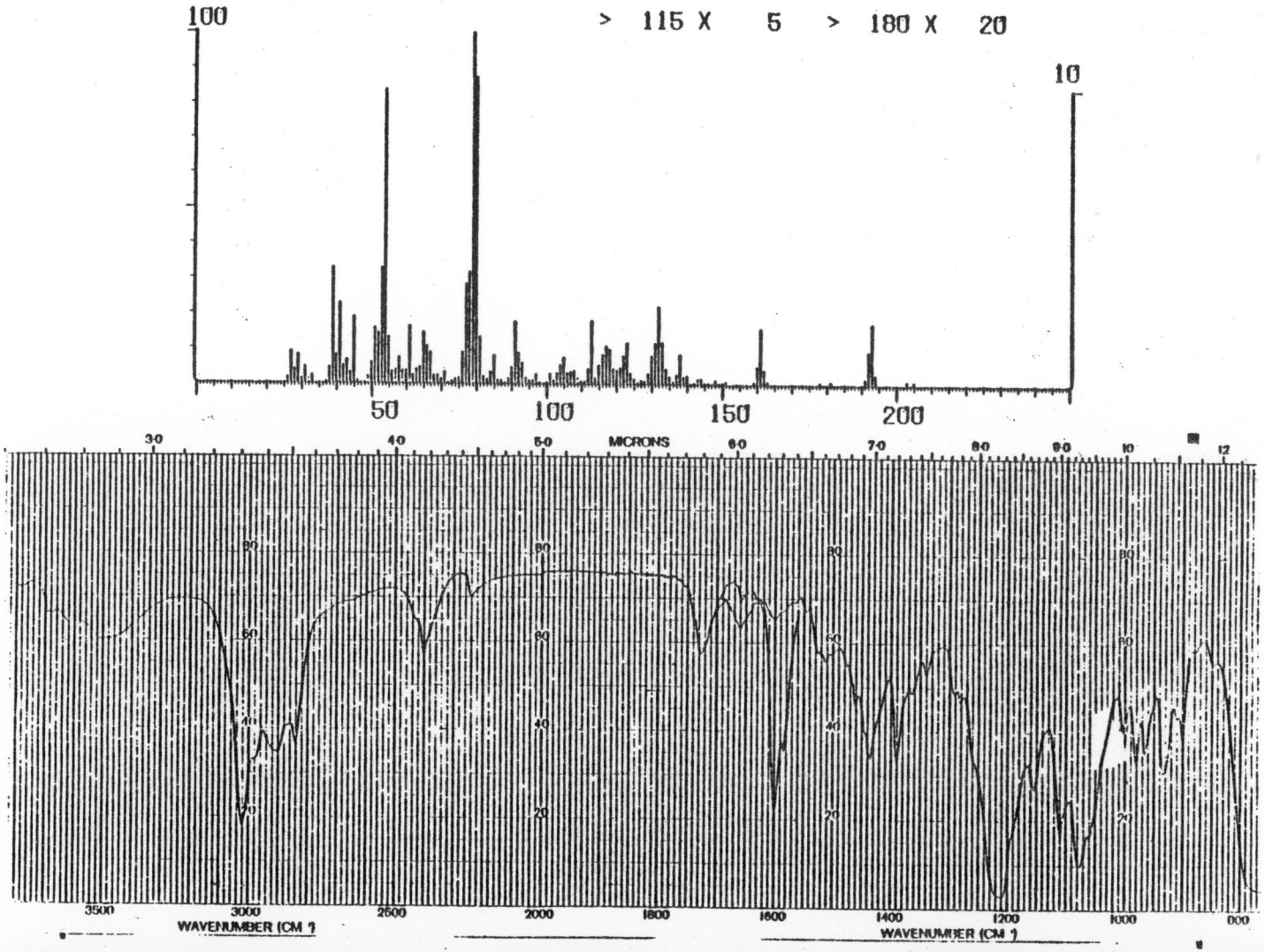

100
50
100
150
200
100
250
300
350

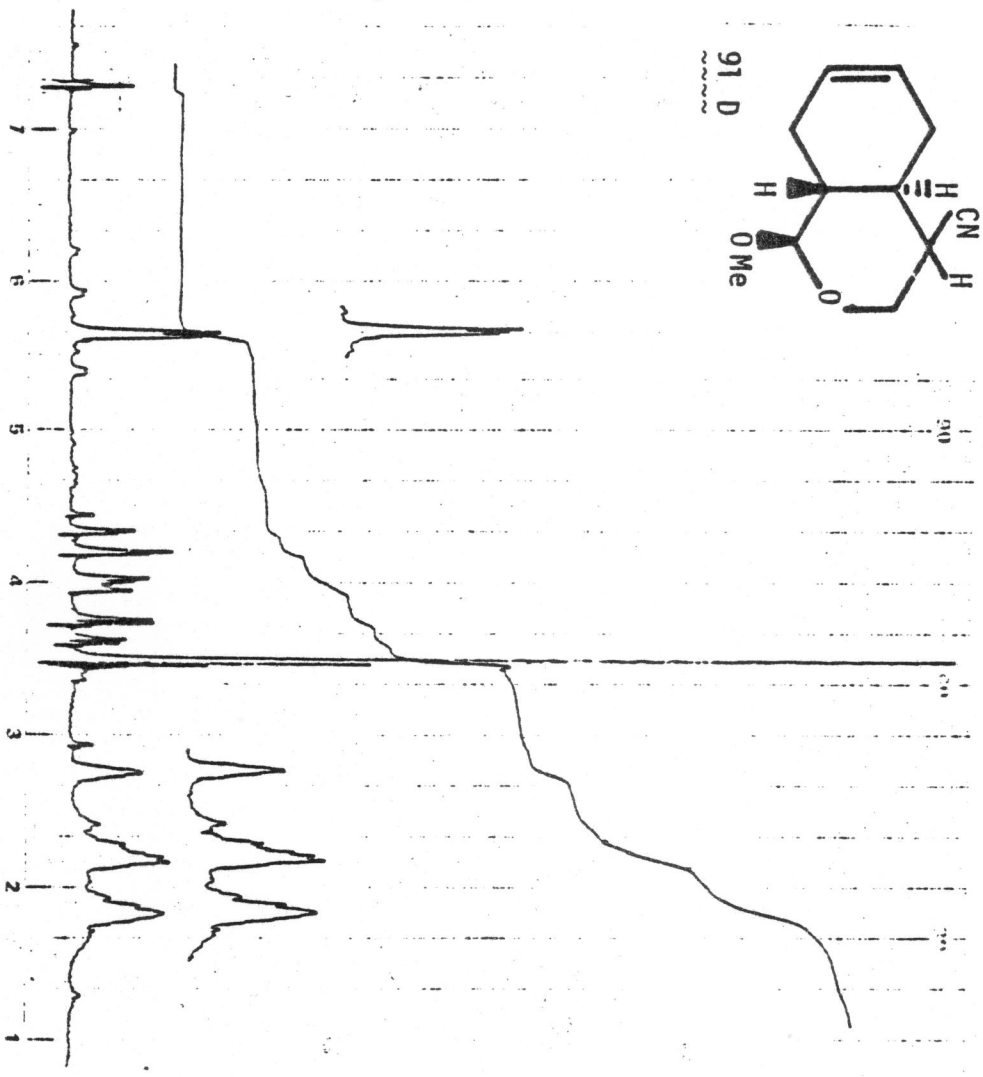
NHNHCO2Me
H
OMe
O
90 B

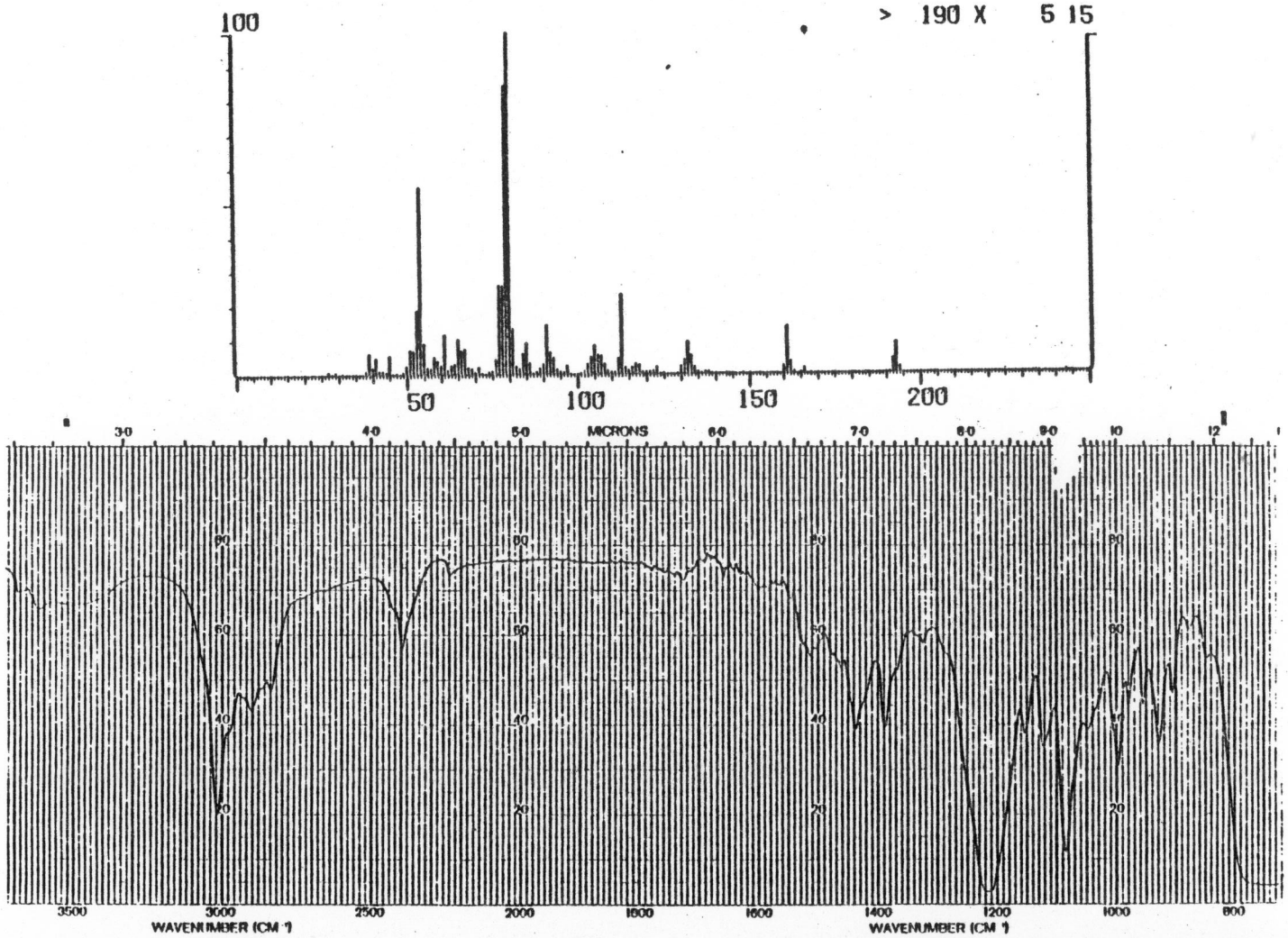

WAVENUMBER (CM-1)
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
MICRONS
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10
12

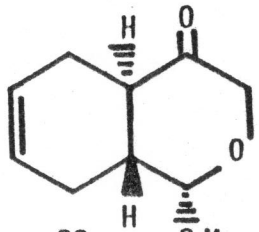

100
50
100
150
200
100 > 270 X 50
250
300


91C
H
H
H
CN
O
O Me
7
6
5
4
3
2
1


100
> 115 X 5 > 180 X 20
10
50
100
150
200
MICRONS
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)


91 D
H
CN
H
OMe
O
7
6
5
4
3
2
1
0.0
1.0
2.0

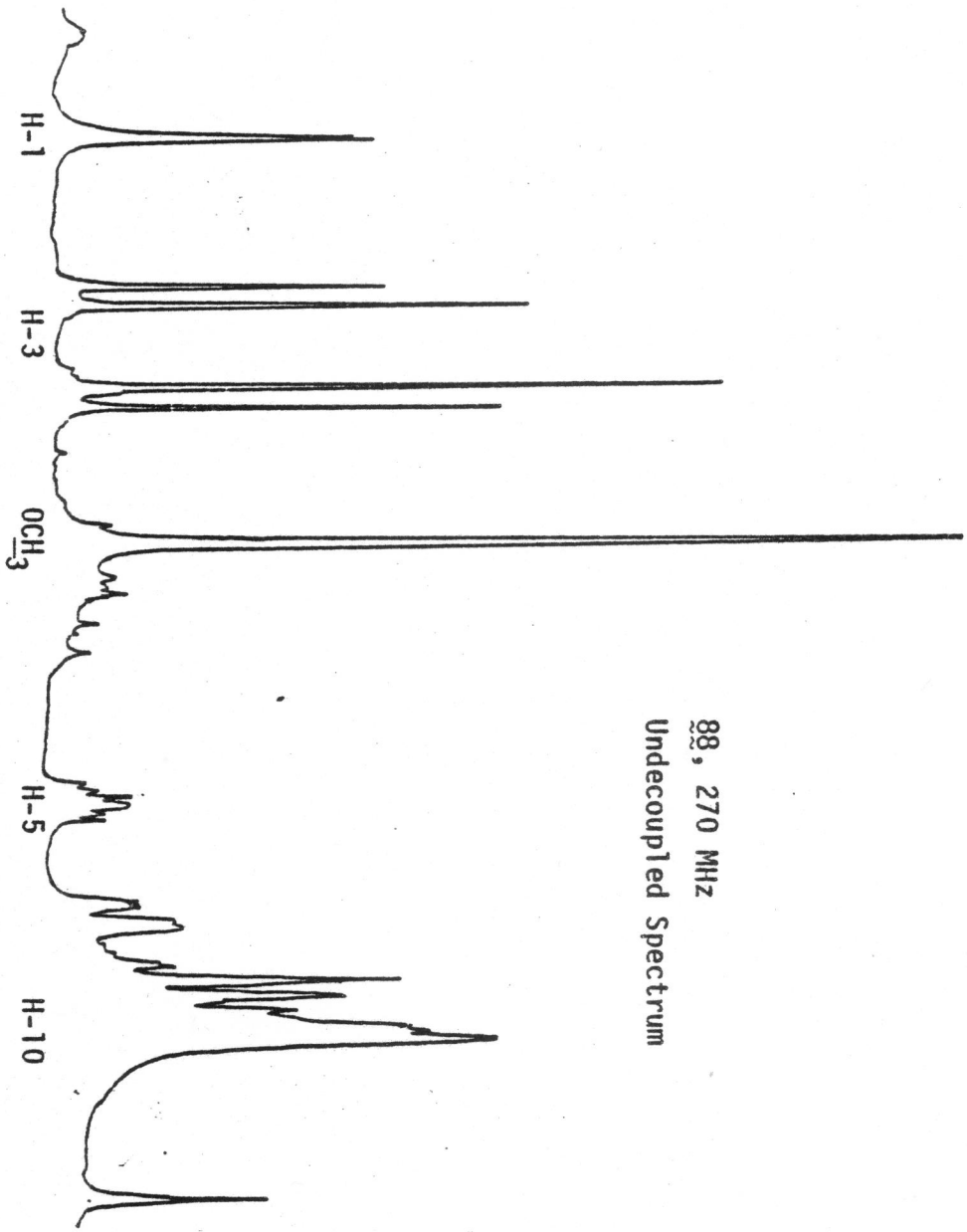

100
> 190 X 5 15
50
100
150
200
MICRONS
WAVENUMBER (CM-1)
WAVENUMBER (CM-1)



88

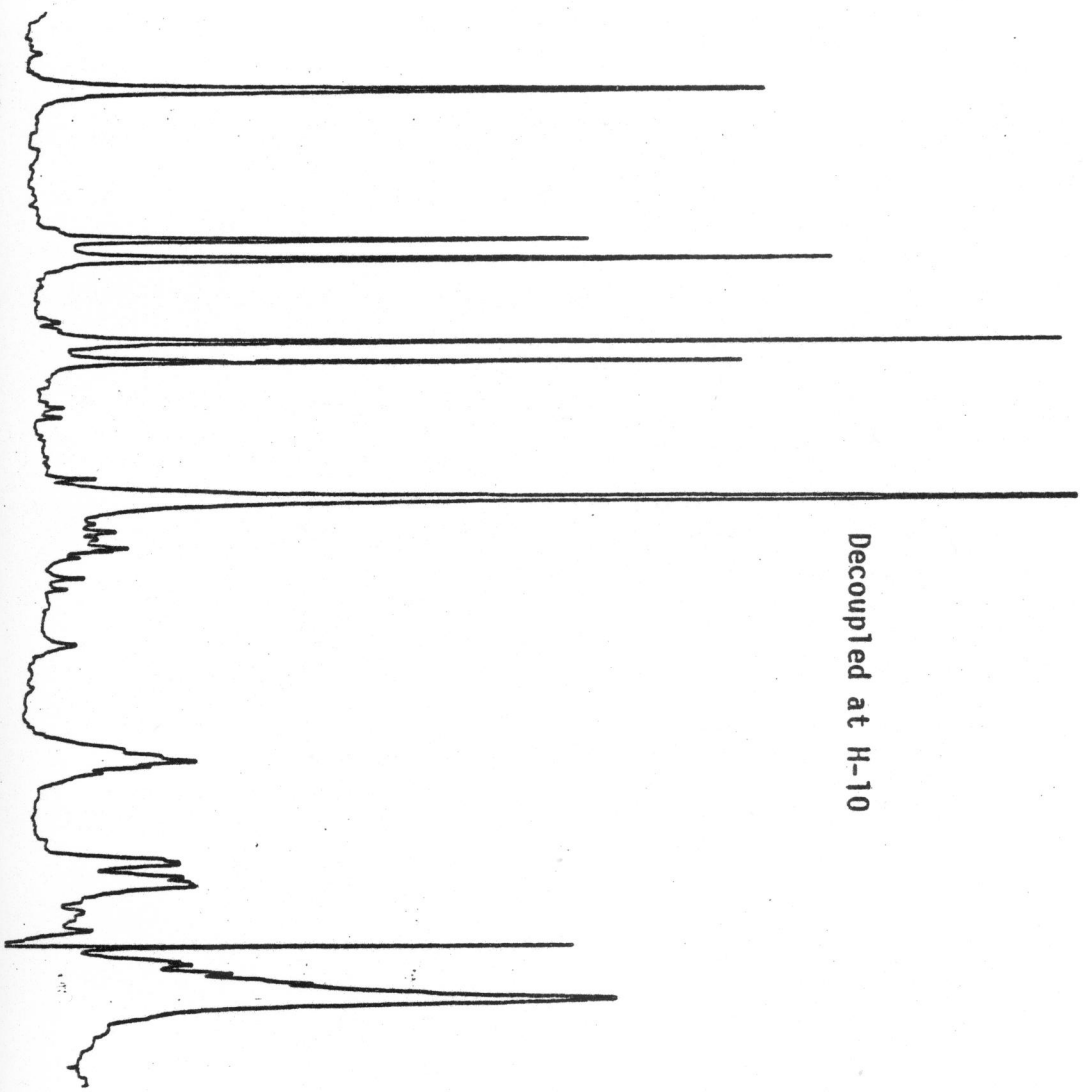
90 MHz

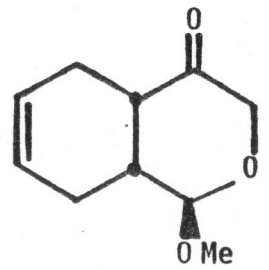
Undecoupled Spectrum



88, 270 MHz
Undecoupled Spectrum

Decoupled at H-10
H-5
Decoupled at H-5
H-10
Decoupled at H-1
H-5
H-10

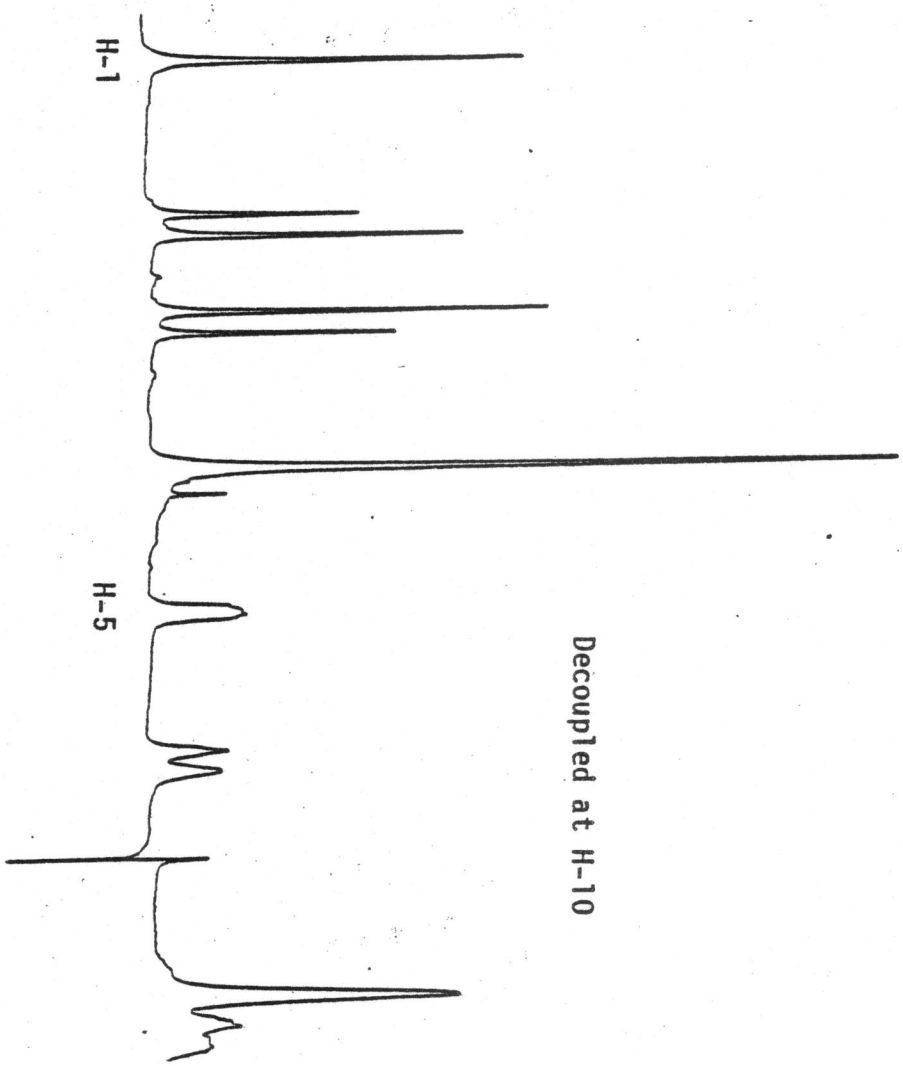

H-1
H-3
OCH3
H-5
Decoupled at H-10



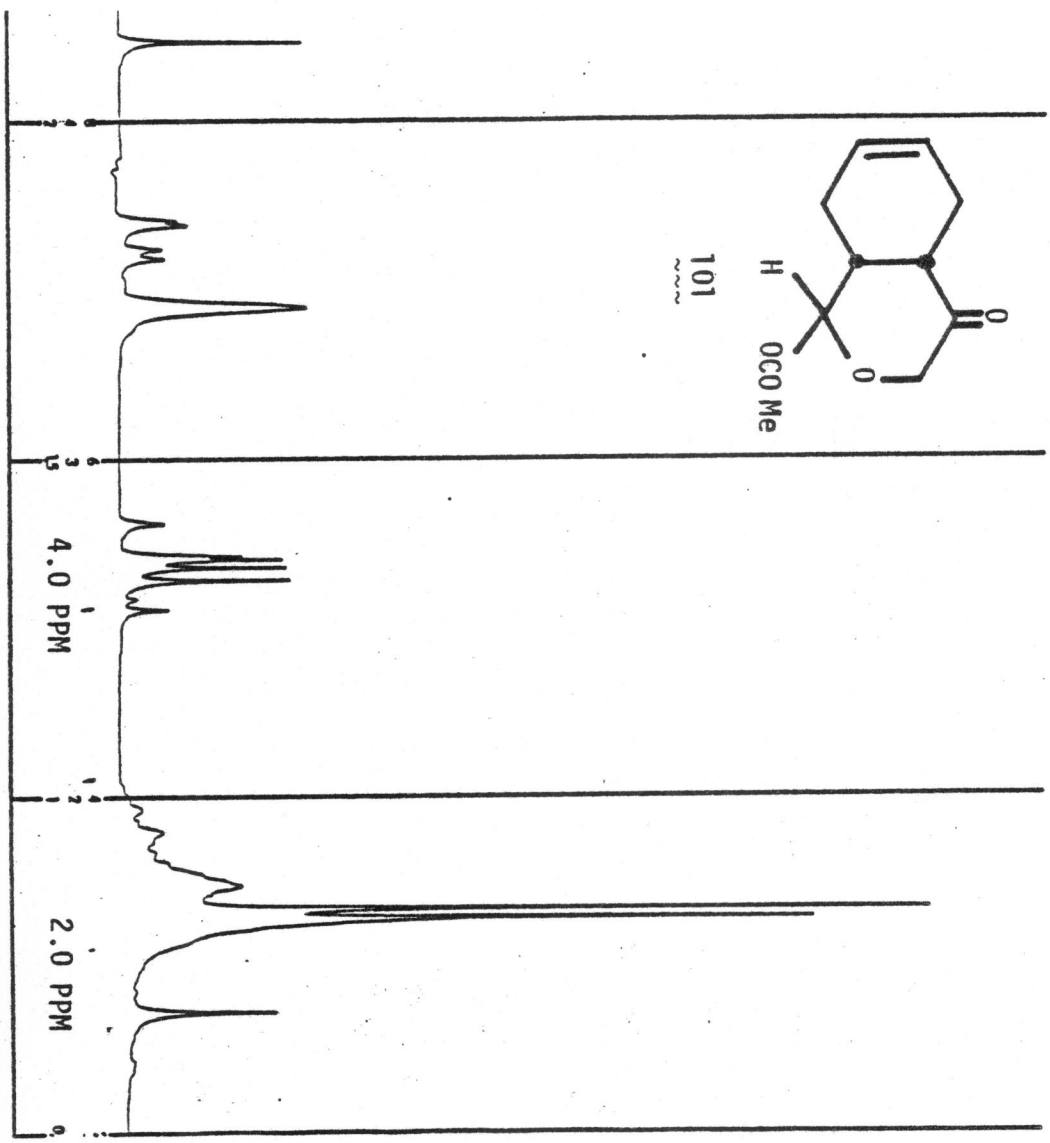
41A 270 MHz

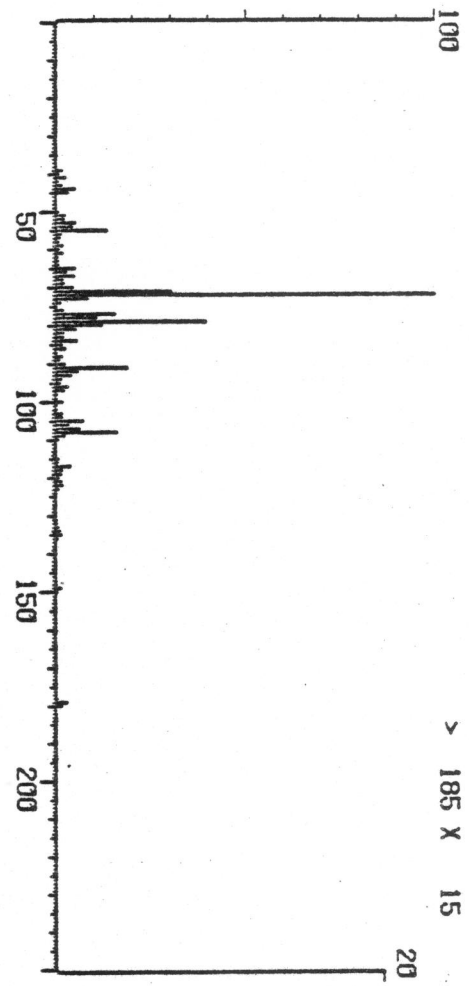
decoupled at H-5

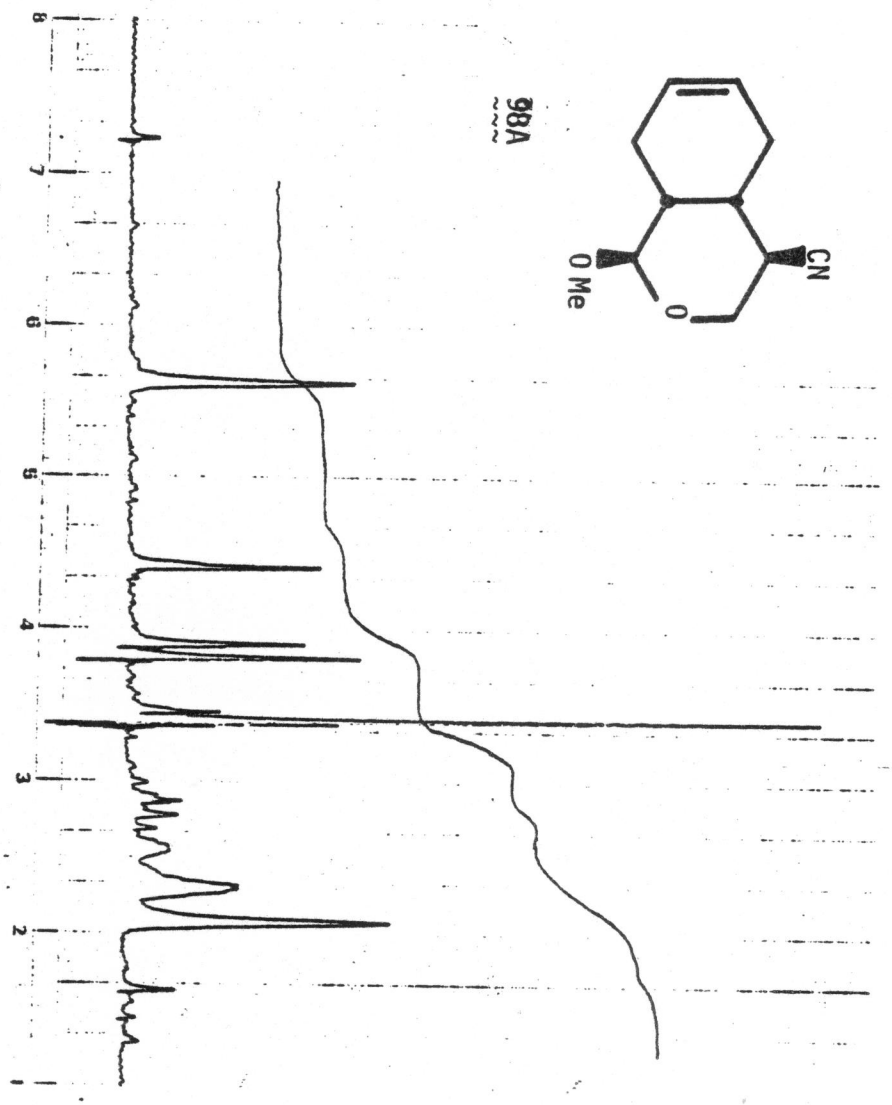
Undecoupled Spectrum


H-1
H-5
Decoupled at H-10

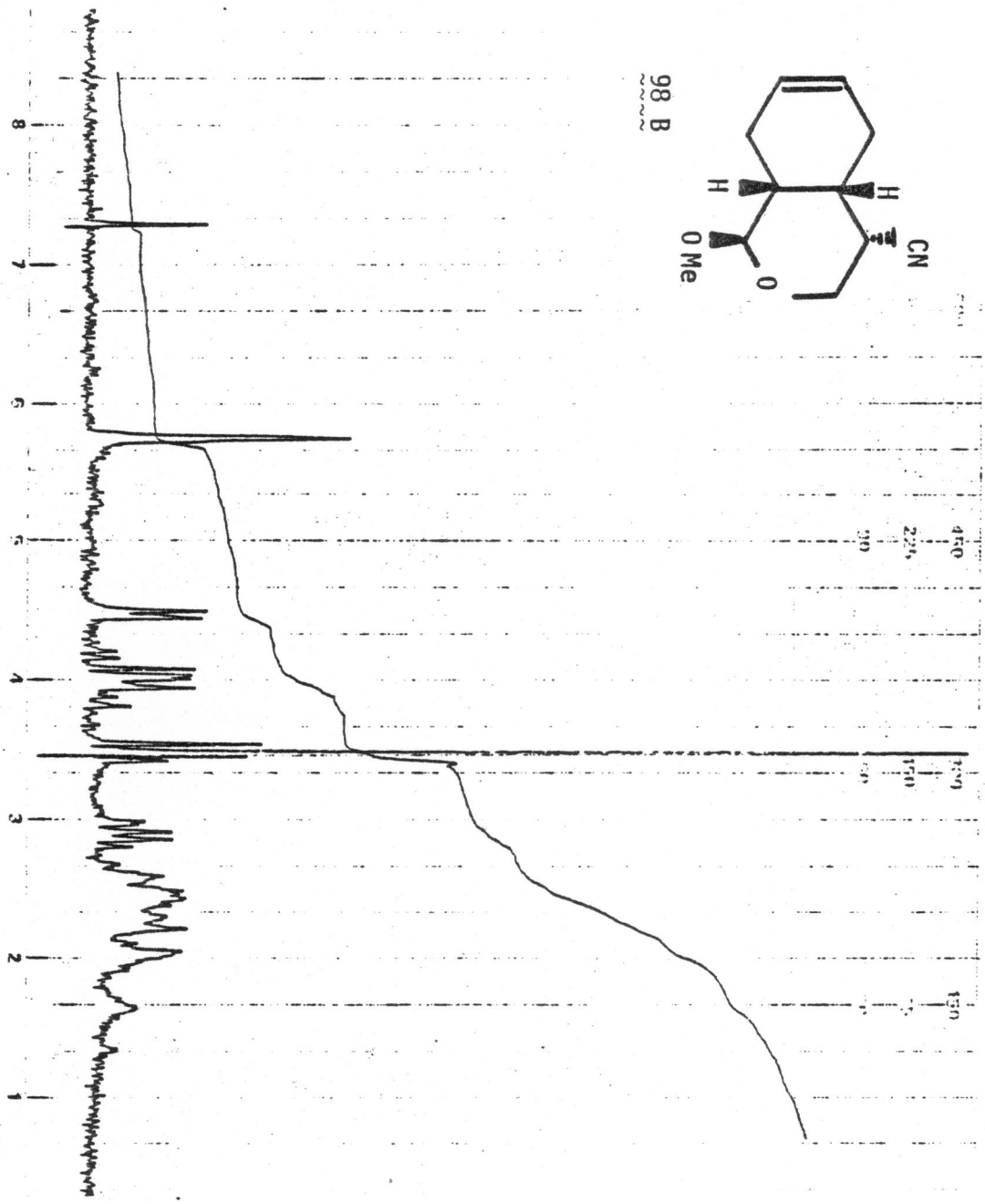
Decoupled at H-1
H-5
H-10

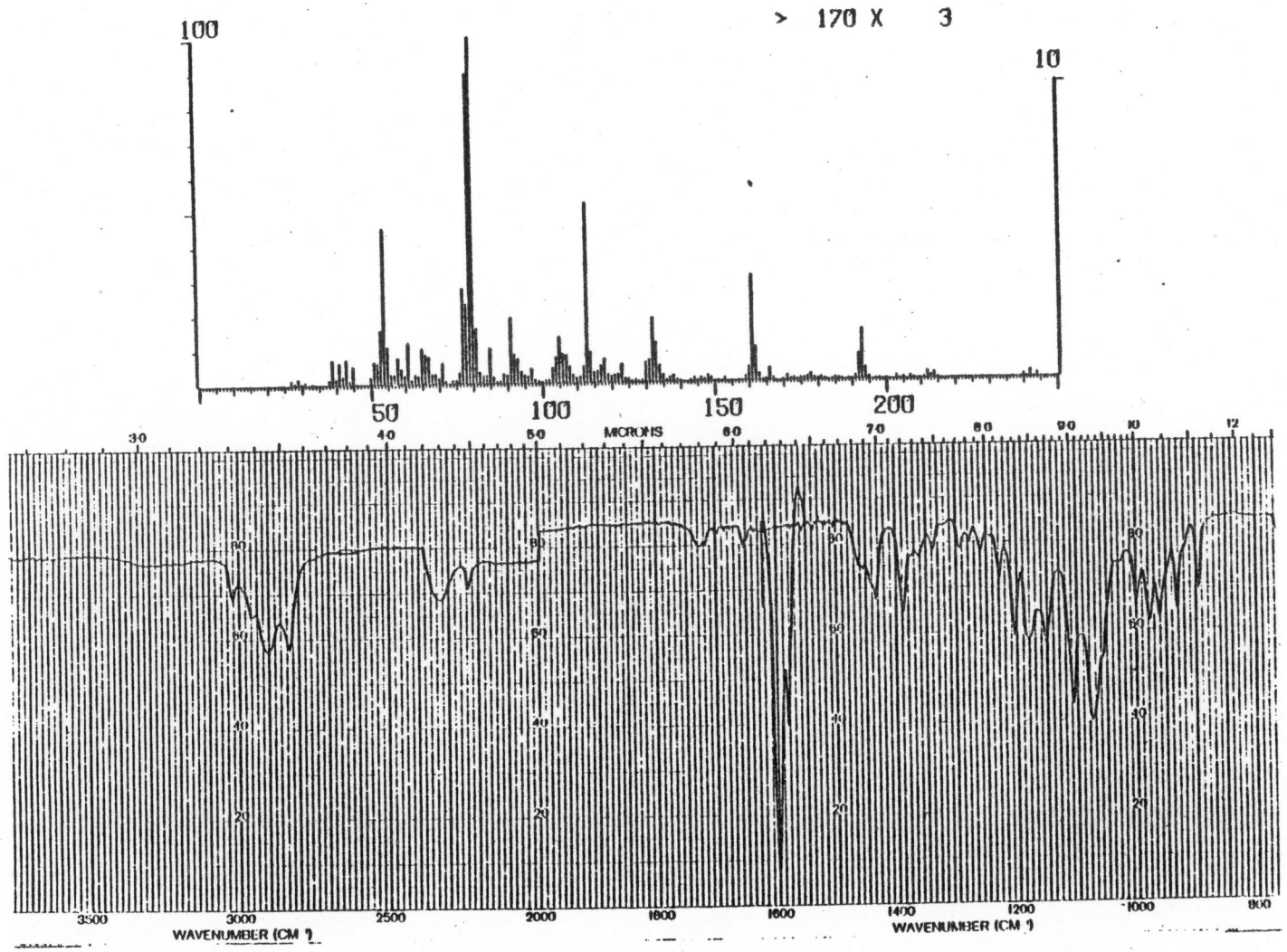

H
OCO Me
O
O
101
4.0 PPM
2.0 PPM

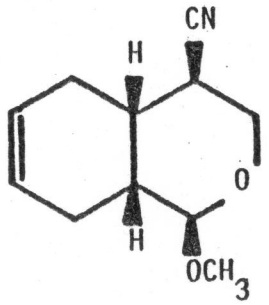

100
50
100
150
200
185 X 15
20


98A
CN
O Me
O
8
7
6
5
4
3
2
1

100
50
100
150
200
> 170 X 5
10
WAVENUMBER (CM-1)
MICRONS


98 B
H
H
O Me
O
CN

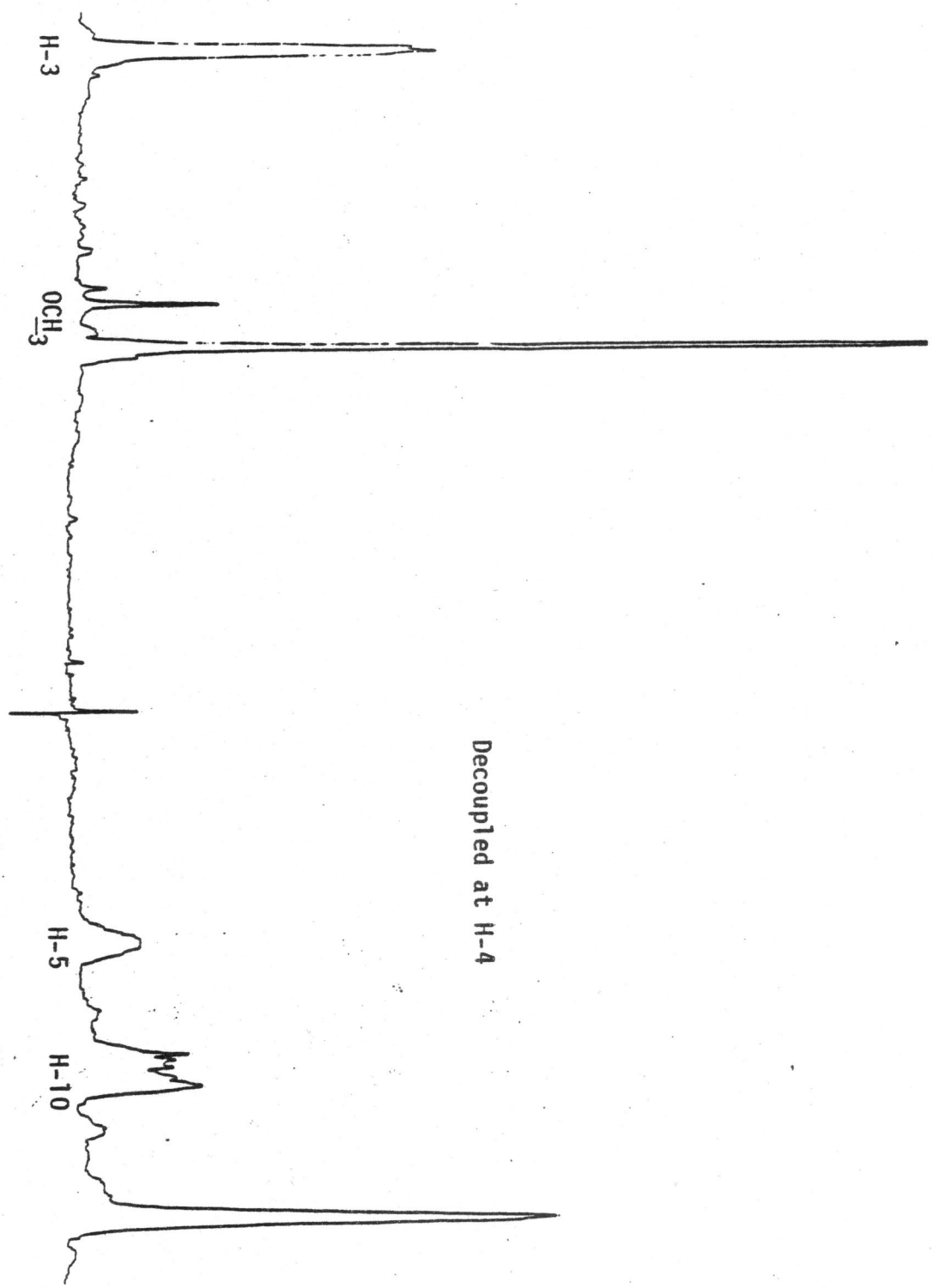

> 170 X 3
100
10
50
100
150
200
MICRONS
WAVENUMBER (CM-1)
WAVENUMBER (CM-1)



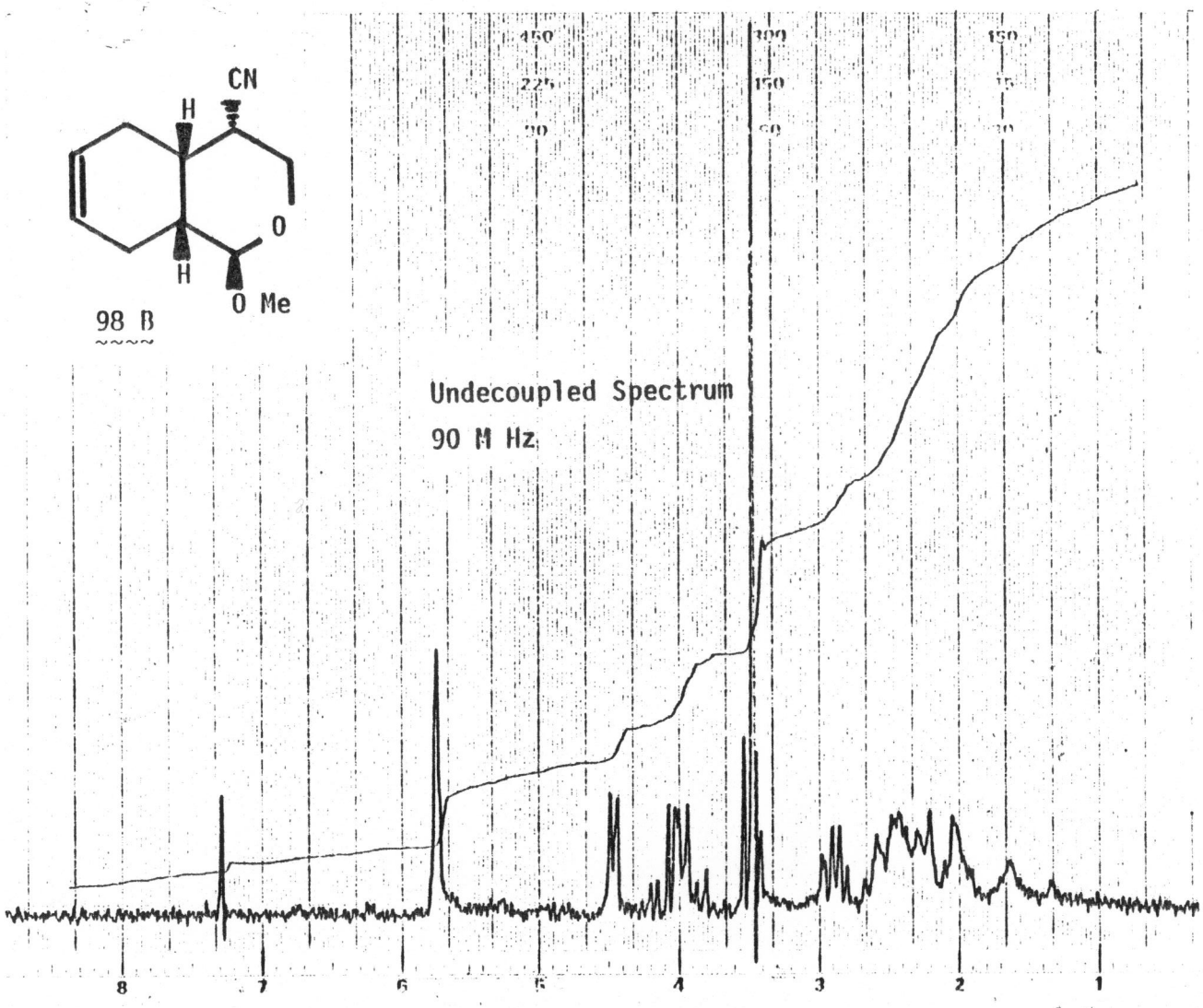
98 A 270 M Hz

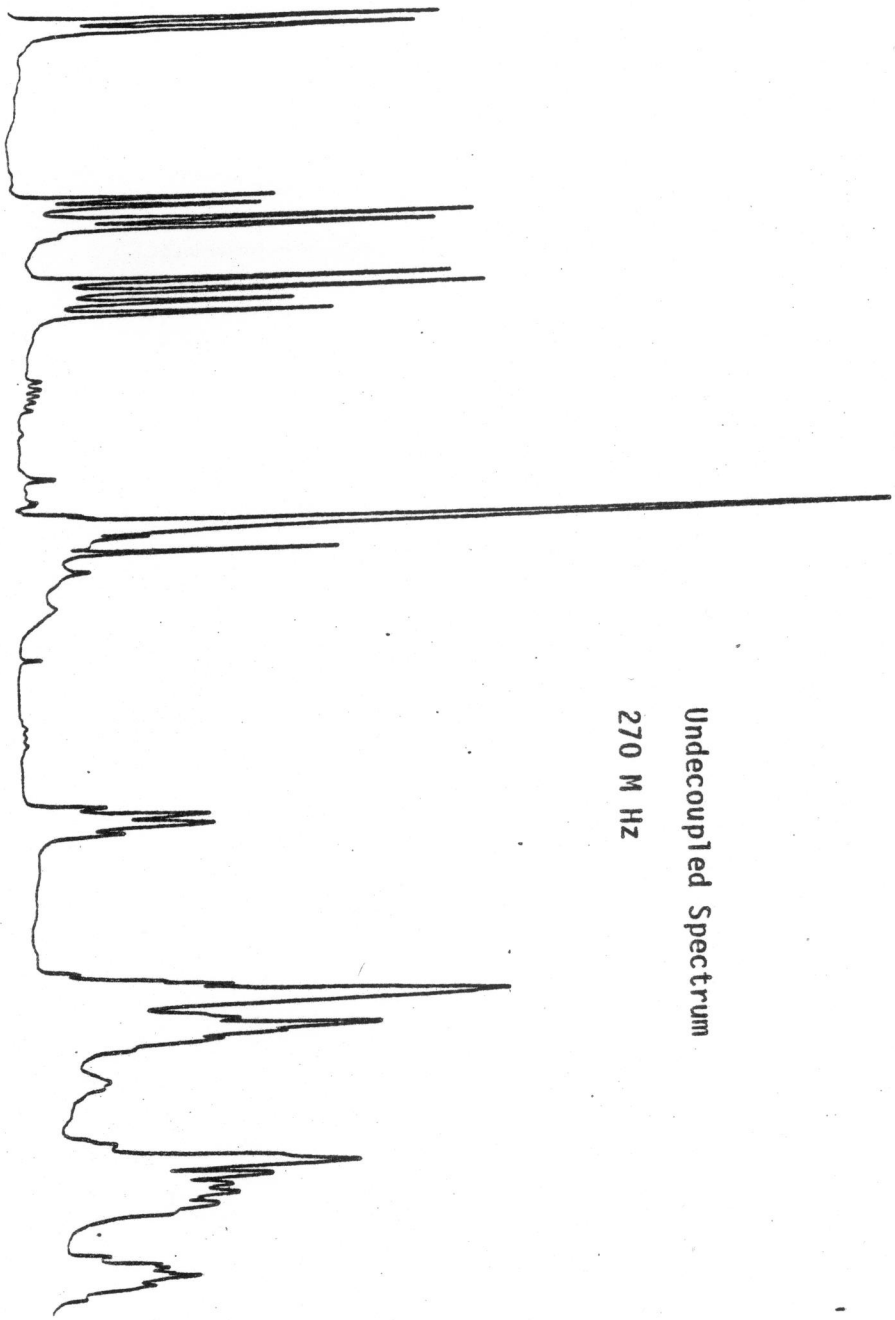
Undecoupled Spectrum

Decoupled at H-4
H-5
H-10
Decoupled at H-1
H-4
H-5
H-10


H-3
OCH3
H-5
H-10
Decoupled at H-4

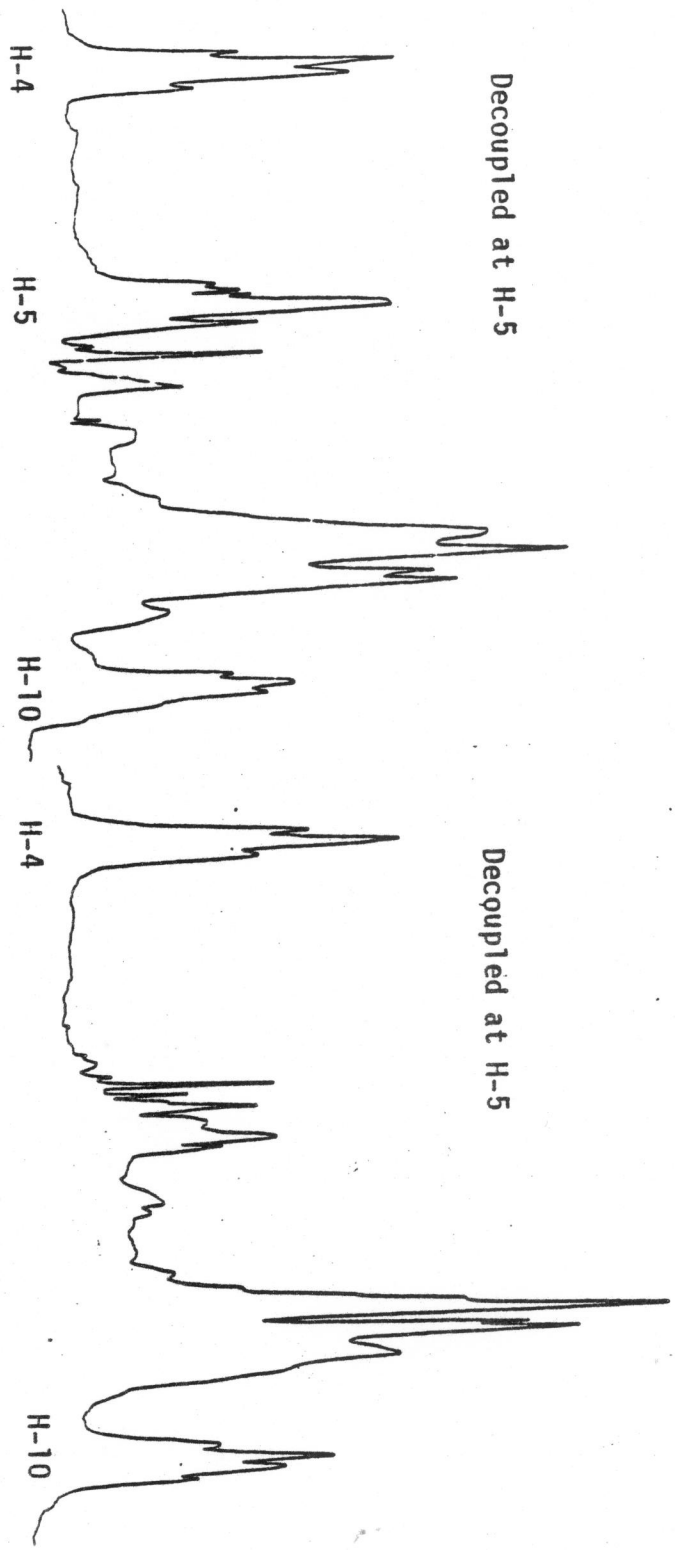
Decoupled at H-5
H-4
H-10
Decoupled at H-1
H-4
H-5
H-10

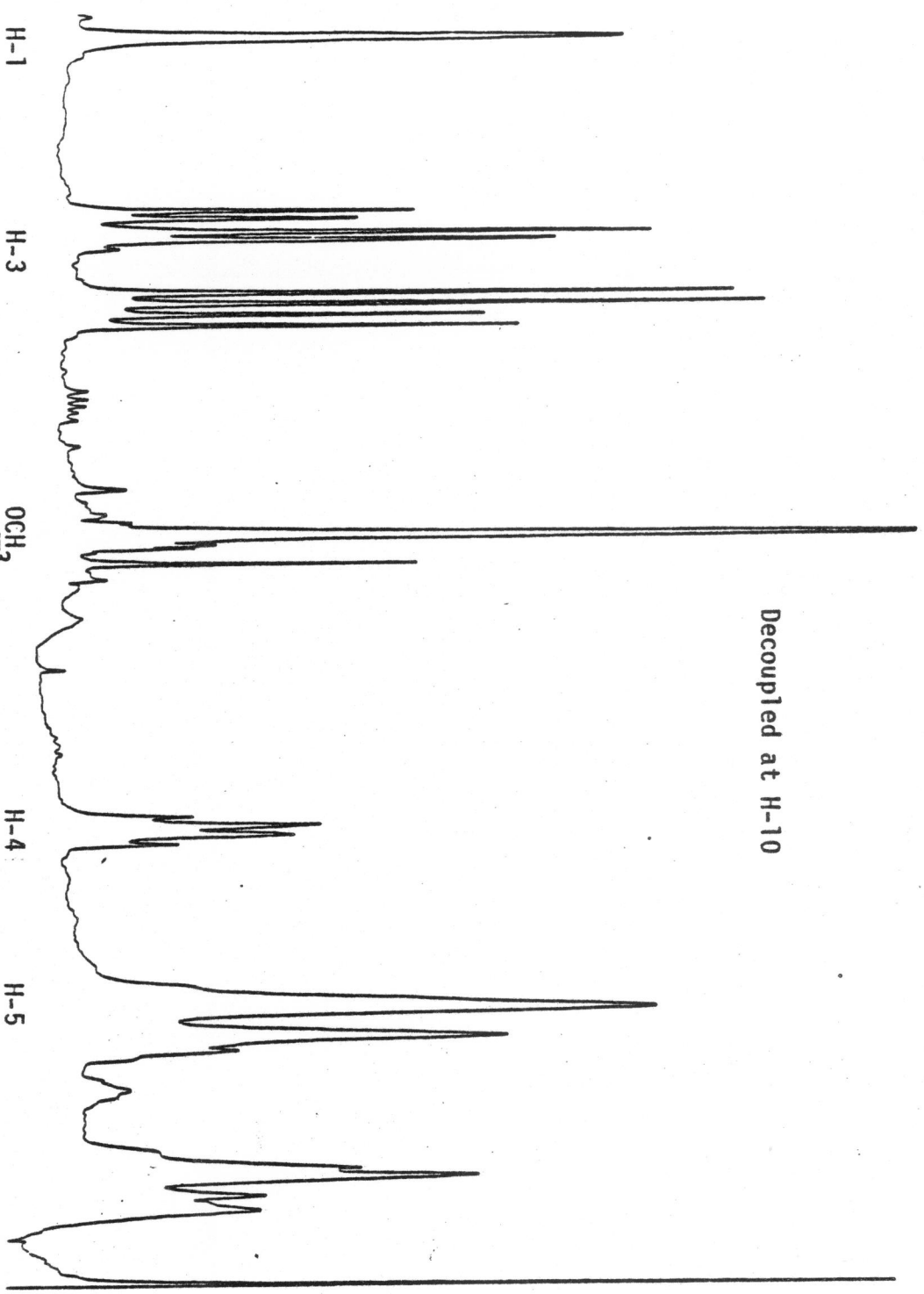

CN
H
O
H
O Me
98 B
Undecoupled Spectrum
90 M Hz
8
7
6
5
4
3
2
1

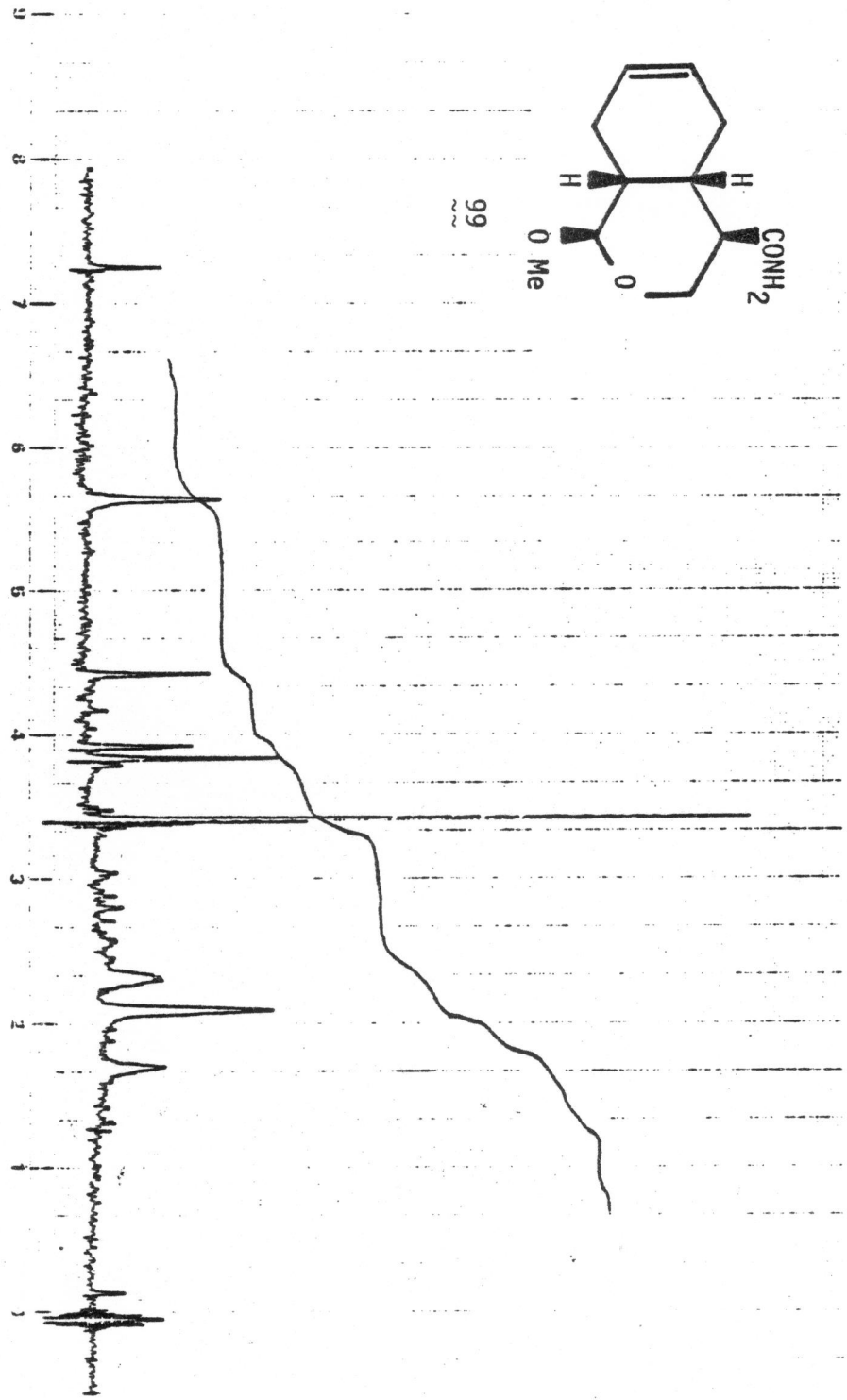


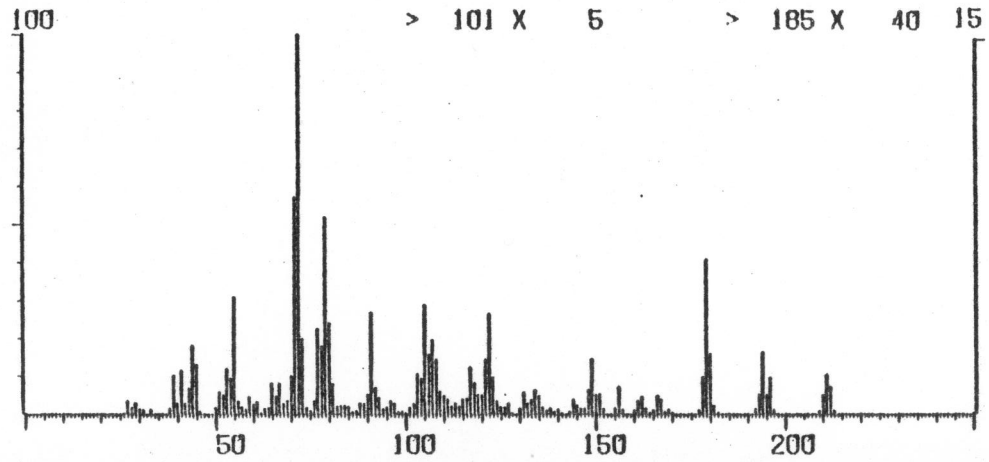
Undecoupled Spectrum

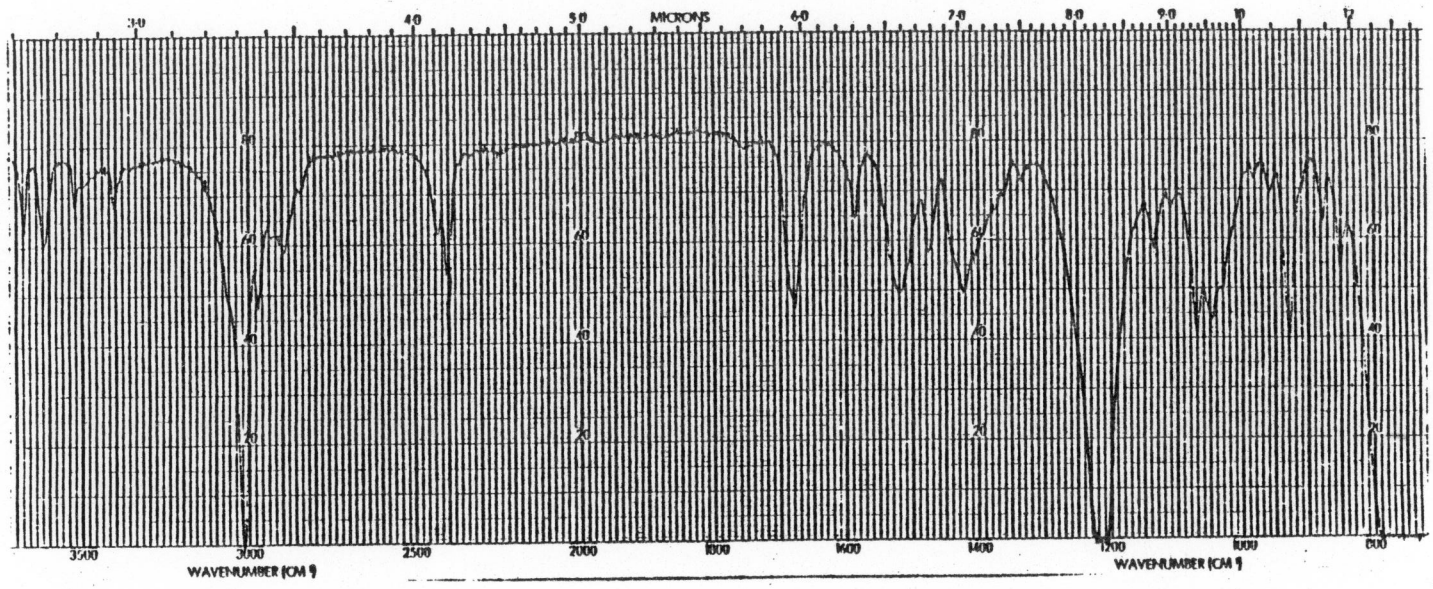
270 M Hz

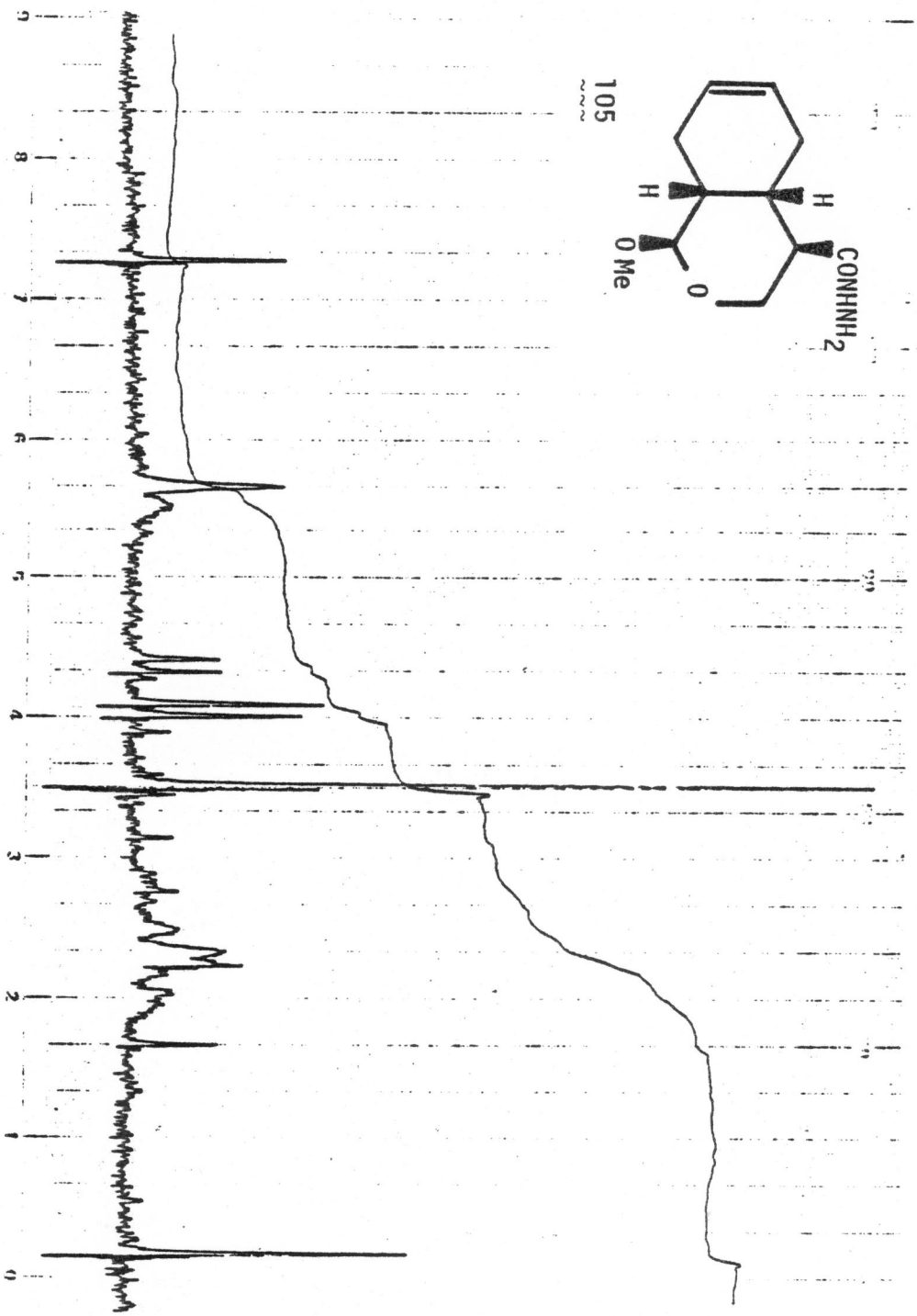

Decoupled at H-5
H-4
H-5
H-10
Decoupled at H-5
H-4
H-10


H-1
H-3
OCH3
H-4
H-5
Decoupled at H-10

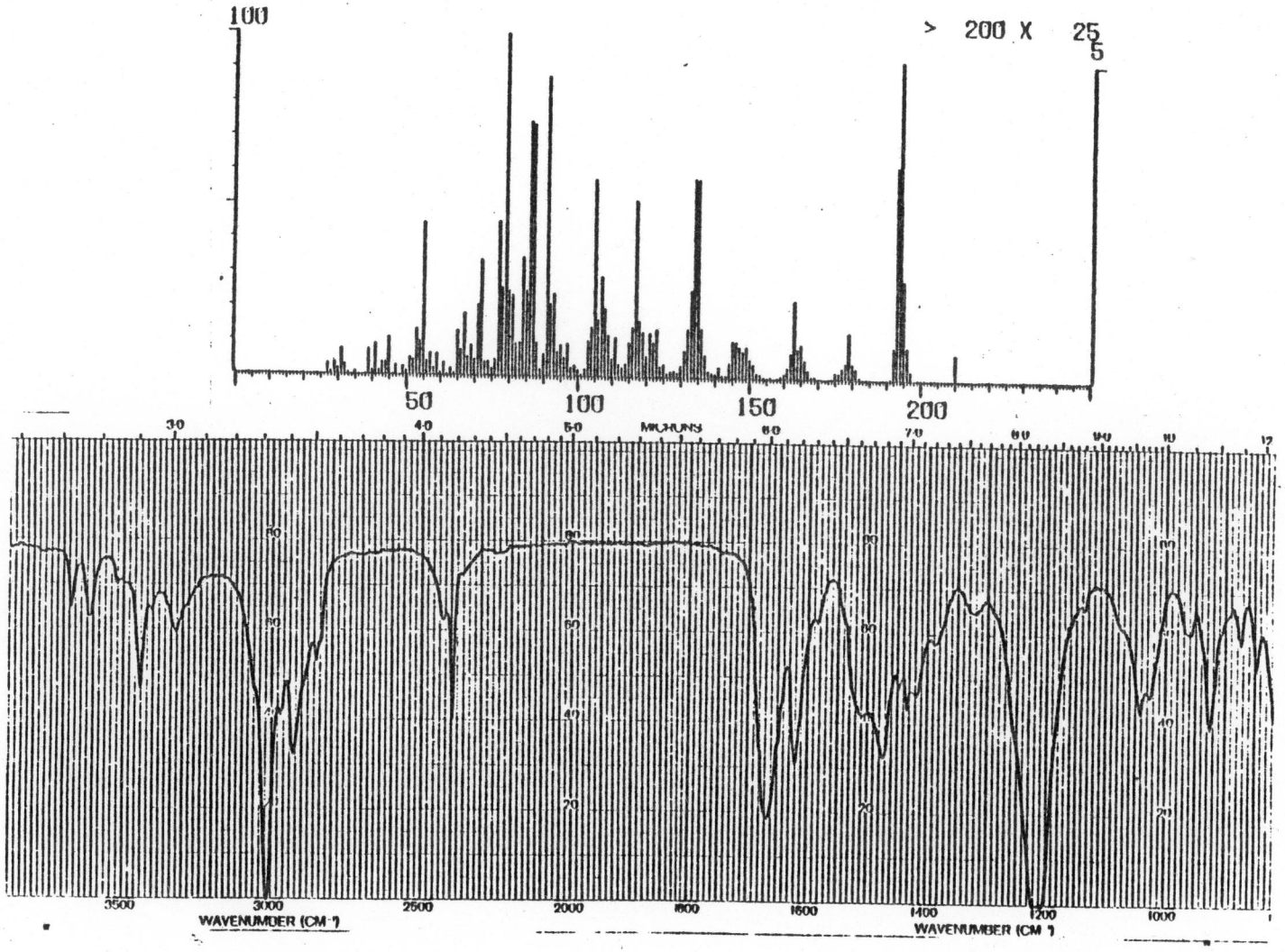

99
~~
H
H
O Me
O
CONH2

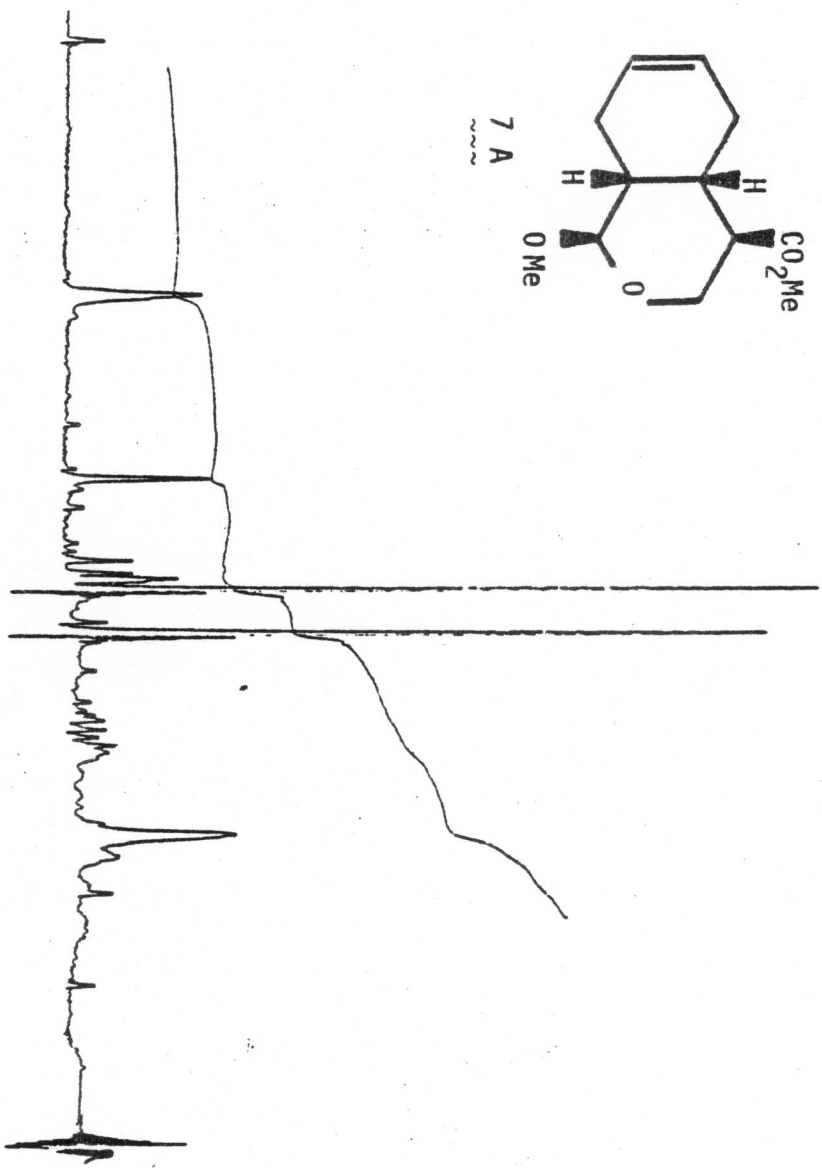

100
> 101 X 5
> 185 X 40 15
50
100
150
200

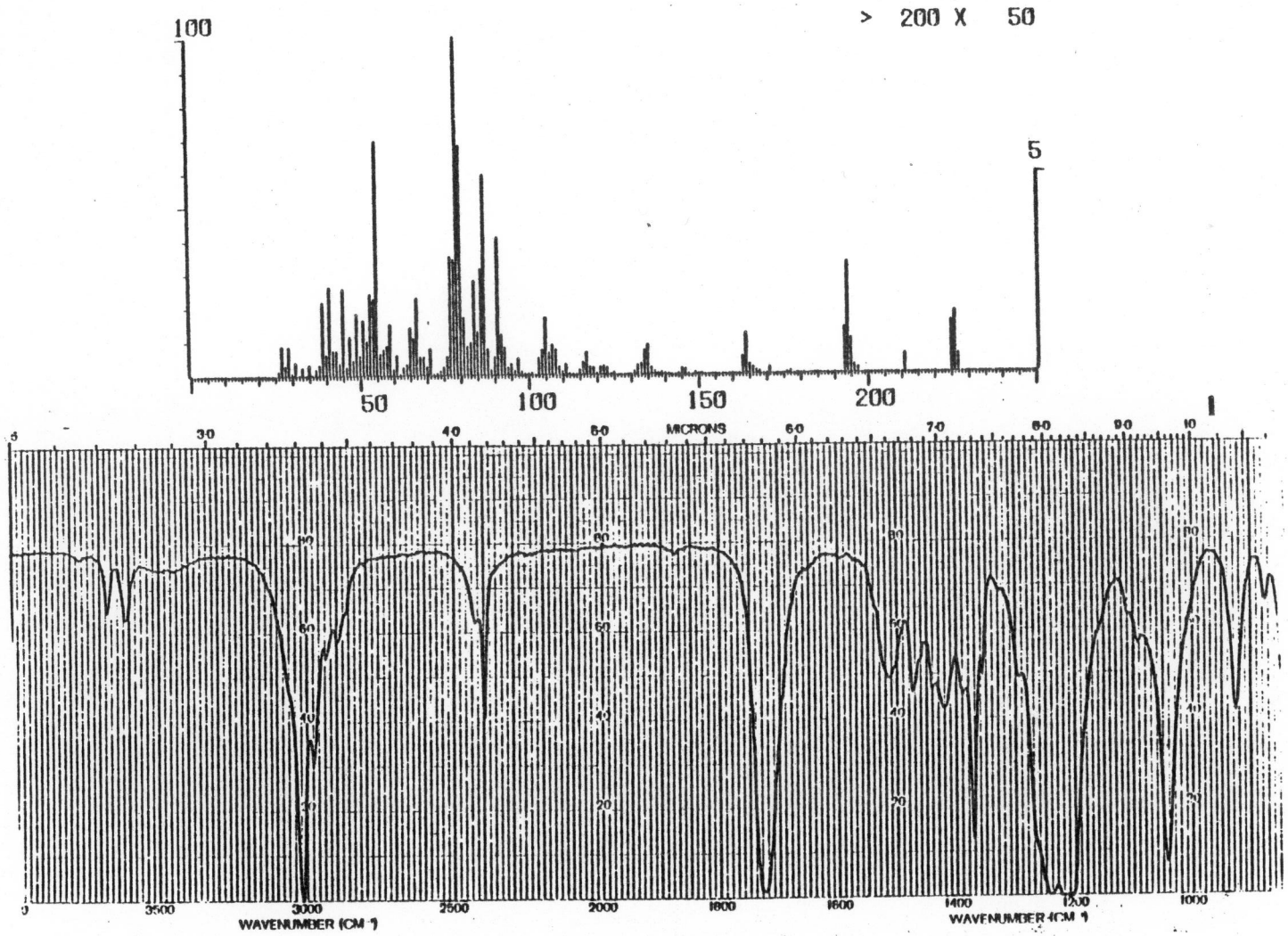

MICRONS
WAVENUMBER (CM-1)
WAVENUMBER (CM-1)



105


100
> 200 X 25
5
50
100
150
200
MICRONS
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)


H
H
OMe
O
CO2Me
7A


> 200 X 50
100
5
50
100
150
200
MICRONS
WAVENUMBER (CM-1)
WAVENUMBER (CM-1)

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